PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]NRA-IMATINIB

Imatinib Mesylate Tablets

Tablets, 100 mg and 400 mg imatinib (as imatinib mesylate), Oral

Protein kinase inhibitor

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RECENT MAJOR LABEL CHANGES

Not Applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART 1: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NRA-IMATINIB (imatinib mesylate) is indicated for:

- the treatment of adult patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia (CML) in chronic phase (see 14 CLINICAL TRIALS).
- the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (CML) in blast crisis or accelerated phase, or in chronic phase after failure of interferon-alpha therapy (see 14 CLINICAL TRIALS).
- use as a single agent for induction phase therapy in adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) (see 14 CLINICAL TRIALS).
- the treatment of adult patients with relapsed or refractory Ph+ALL as monotherapy (see 14 CLINICAL TRIALS).
- the treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements (see 14 CLINICAL TRIALS).
- the treatment of adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with NRA-IMATINIB may be considered if there is no satisfactorily response to other therapies (see 14 CLINICAL TRIALS).
- the treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement (see 14 CLINICAL TRIALS).
- the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (see 14 CLINICAL TRIALS).
- the treatment of adult patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) (see 14 CLINICAL TRIALS).
- the adjuvant treatment of adult patients who are at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST (see 14 CLINICAL TRIALS).

[1] ASM: Aggressive systemic mastocytosis; SM-AHNMD: Systemic mastocytosis with an associated clonal hematological non-mast-cell disorder.

1.1 Pediatrics

Pediatrics (<18 years of age): Health Canada has authorized an indication for pediatric use for

the treatment of pediatric patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia (CML) in chronic phase (see 7.1.3 Pediatrics).

There is no experience with the use of imatinib mesylate in pediatric patients with CML under 2 years of age. There is very limited to no experience with the use of imatinib mesylate in pediatric patients in other indications.

1.2 Geriatrics

Geriatrics (≥65 years of age):

No clinically meaningful differences in effectiveness was observed between older and younger patients in the CML phase II study (see 7.1.4 Geriatrics).

No clinically meaningful differences in safety was observed between older and younger patients in the adjuvant GIST study (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- NRA-IMATINIB is contraindicated in patients with hypersensitivity to imatinib or to any other component of NRA-IMATINIB (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

NRA-IMATINIB should only be administered under the supervision of a physician experienced with the use of chemotherapy and with treatment of hematological malignancies and/or malignant sarcomas including gastrointestinal stromal tumors (GISTs) and dermatofibrosarcoma protuberans (DFSP).

The following are significant adverse drug reactions identified in clinical trials conducted with imatinib mesylate:

- Severe congestive heart failure (CHF) and reduction of left ventricular ejection fraction (LVEF) have been observed (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).
- Rhabdomyolysis has been rarely observed (see 8.5 Post-Market Adverse Reactions).
- Severe hemorrhages may occur (see 7 WARNINGS AND PRECAUTIONS - General).
- Fluid retention may occur (see 7 WARNINGS AND PRECAUTIONS - General).
- Liver failure (in some cases, fatal) may occur (see 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic).
- Gastrointestinal perforation (in some cases, fatal) may occur (see 7 WARNINGS AND PRECAUTIONS - Gastrointestinal).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Therapy should be administered under the supervision of a physician experienced in the treatment of patients with hematological malignancies and/or malignant sarcomas.

The prescribed dose should be administered orally, during a meal and with a large glass of water to minimize the risk of gastrointestinal disturbances. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day in the morning and in the evening. Efficacy data for the 800 mg/day dose are limited.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet, and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s). Traces of the disintegrated tablet left in the glass after drinking should also be consumed.

Treatment should be continued as long as the patient continues to benefit.

Tumour Lysis Syndrome (TLS)

Preventative measures should be considered prior to treatment with NRA-IMATINIB in patients with increased risk for TLS (See 7 WARNINGS AND PRECAUTIONS - General and 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests).

Iron Exposure

For daily dosing of 800 mg, NRA-IMATINIB should be administered using the 400 mg tablet twice a day to reduce exposure to iron.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Chronic myeloid leukemia (CML)

The recommended dosage of NRA-IMATINIB is 400 mg/day for adult patients with newly diagnosed CML or in chronic phase CML. The recommended dosage for adult patients in accelerated phase or blast crisis is 600 mg/day. The recommended dosage of NRA-IMATINIB for pediatric patients with newly diagnosed Ph+ CML is 340 mg/m^2/day (rounded to the nearest 100 mg, i.e. not to exceed 600 mg).

In CML, a dose increase from 400 mg to 600 mg or to 800 mg/day in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reactions and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to NRAieve a satisfactory hematologic response after at least 3 months of treatment; failure to NRAieve a cytogenetic response after

12 months of treatment; or loss of a previously NRAieved hematologic and/or cytogenetic response.

Patients with CML should undergo regular response monitoring (see 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests). Any changes to patient imatinib therapy (for example, when imatinib dose is lowered due to occurrence of side effects) should be followed by close response monitoring.

Ph+ Acute Lymphoblastic Leukemia (Ph+ALL)

The recommended dose of NRA-IMATINIB for use as a single-agent for induction phase therapy in adult patients with newly diagnosed Ph+ALL, or for adult patients with relapsed or refractory Ph+ ALL is 600 mg/day.

Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

The recommended dose of NRA-IMATINIB is 400 mg/day for adult patients with MDS/MPD.

Aggressive sub-types of Systemic Mastocytosis (ASM and SM-AHNMD)

The recommended dose of NRA-IMATINIB is 400 mg/day for adult patients with ASM or SM-AHNMD without the D816V c-Kit mutation or mutational status unknown and not responding satisfactory to other therapies.

For patients with ASM or SM-AHNMD associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended. A dose increase from 100 mg to 400 mg for these patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)

The recommended dose of NRA-IMATINIB is 100 mg/day for adult patients with HES/CEL.

For HES/CEL patients, a dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Treatment should be continued as long as the patient continues to benefit.

Dermatofibrosarcoma Protuberans (DFSP)

The recommended dose of NRA-IMATINIB is 800 mg/day for adult patients with DFSP.

Gastrointestinal Stromal Tumors (GIST), Unresectable and/or metastatic malignant GIST

The recommended dose of NRA-IMATINIB is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic malignant GIST, depending on the stage and the progression of the disease. In GIST, a dose increase from 400 mg/day to 600 mg/day or to 800 mg/day for adult patients may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

Adjuvant Treatment of GIST

The recommended dose of NRA-IMATINIB is 400 mg/day for the adjuvant treatment of adult patients at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST. In the clinical study, imatinib mesylate was administrated for one year. The optimal treatment duration with imatinib mesylate is not known.

No dose adjustment of the initial 400 mg a day dose was made in patients with GIST with mild liver function abnormalities.

Dosage Adjustment

Hepatotoxicity and Other Non-Hematologic Adverse Drug Reactions

If a severe non-hematologic adverse drug reaction develops (such as severe hepatotoxicty or severe fluid retention), NRA-IMATINIB should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, NRA-IMATINIB should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with NRA-IMATINIB may then be continued at a reduced daily dose (i.e., from 400 mg to 300 mg or from 600 mg to 400 mg, or from 800 mg to 600 mg). In pediatric patients, daily doses can be reduced under the same circumstances from 340 mg/m^2/day to 260 mg/m^2/day.

Hepatic Impairment

Patients with mild, and moderate liver dysfunction should be dosed at the minimum effective dose of 400 mg daily and patients with severe liver dysfunction should start at 200 mg daily. In the absence of severe toxicity, a dose increase up to 300 mg daily may be considered. The dose should be reduced if the patient develops unacceptable toxicity (see 10.3 Pharmacokinetics – Hepatic Insufficiency).

Renal Impairment

Imatinib mesylate and its metabolites are not excreted via the kidney to a significant extent. However, it has been shown that exposure to imatinib is increased up to 2-fold in patients with mild (CrCL: 40-59 mL/min) and moderate (CrCL: 20-39 mL/min) renal dysfunction, and that there is a significant correlation in the incidence of serious adverse events with decreased renal function.

In clinical trials to date, the safety and efficacy of imatinib mesylate in patients with renal impairment has not been established. Patients with mild or moderate renal dysfunction should be treated with caution, and be given the minimum recommended effective dose of 400 mg daily as starting dose (see 10.3 Pharmacokinetics – Renal Insufficiency). The dose should be reduced if not tolerable. If tolerated, the dose can be increased for lack of efficacy (see section 7 WARNINGS AND PRECAUTIONS - Renal). Treatment of patients with moderate renal insufficiency at 800 mg cannot be recommended as this dose has not been investigated in

these patients. The effect of imatinib mesylate treatment on patients with severe renal dysfunction (CrCL: <20 mL/min) and on hemodialysis has not been assessed, so treatment of these patients with imatinib cannot be recommended.

Pediatric Populations

Dosing in pediatric patients should be on the basis of body surface area (mg/m^2). Treatment can be given as a once daily dose or alternatively the daily dose may be split into two administrations – one in the morning and one in the evening (see 14.1 Clinical Trials by Indication - Pediatric newly diagnosed chronic myeloid leukemia and 10.3 Pharmacokinetics - Pediatrics). There is no experience with the use of imatinib mesylate in pediatric patients with CML under 2 years of age. There is very limited to no experience with the use of imatinib mesylate in pediatric patients in other indications.

Hematologic adverse drug reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 1.

Table 1 Dose adjustments for neutropenia and thrombocytopenia.

ASM or SM-AHNMD associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg)	ANC < 1.0 x10^9/L and/or platelets <50 x10^9/L	1. Stop NRA-IMATINIB until ANC[3] 1.5 x10^9/L and platelets[3] 75 x10^9/L. 2. Resume treatment with NRA-IMATINIB at previous dose (i.e. before severe adverse drug reaction).
Chronic phase CML (starting at dose 400 mg) MDS/MPD, ASM/SM-AHNMD, HES/CEL (at 400 mg dose) or GIST (starting dose either 400 mg or 600 mg)	ANC < 1.0 x10^9/L and/or platelets <50 X 10^9/L	1. Stop NRA-IMATINIB until ANC[3] 1.5 x10^9/L and platelets[3] 75 x10^9/L. 2. Resume treatment with NRA-IMATINIB at the original dose of 400 mg or 600 mg (i.e. before severe adverse drug reaction). 3. If recurrence of ANC<1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume NRA-IMATINIB at a reduced dose of 300 mg (if starting dose was 400 mg, 400 mg if starting dose was 600 mg).
Newly diagnosed pediatric chronic phase CML (at dose 340 mg/m^2/day)	ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L	1. Stop NRA-IMATINIB until ANC[3] 1.5 x10^9/L and platelets[3] 75 x10^9/L. 2. Resume treatment with NRA-IMATINIB at previous dose (i.e. before severe adverse drug reaction). 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume NRA-IMATINIB at reduced dose of 260 mg/m^2/day.

Accelerated phase CML and blast crisis and Ph+ALL (starting dose 600 mg)	[1]ANC < 0.5 x10^9/L and/or platelets <10 x10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, reduce dose of NRA-IMATINIB to 400 mg. 3. If cytopenia persists for 2 weeks, reduce further to 300 mg. 4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop NRA-IMATINIB until ANC ≥1 x10^9/L and platelets ≥20 x10^9/L and then resume treatment at 300 mg.
DFSP (at 800 mg dose)	ANC < 1.0 x10^9/L and/or platelets <50x10^9/L	1. Stop NRA-IMATINIB until ANC[3] 1.5 x10^9/L and platelets[3] 75 x10^9/L. 2. Resume treatment with NRA-IMATINIB at 600 mg. 3. In the event of recurrence of ANC < 1.0 x10^9/L and/or platelets < 50 x10^9/L, repeat step 1 and resume NRA-IMATINIB at reduced dose of 400 mg.

ANC: absolute neutrophil count
[1]occurring after at least 1 month of treatment

4.5 Missed Dose

If a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.

5 OVERDOSE

Experience with higher than therapeutic doses is limited. Isolated cases of imatinib mesylate overdosage have been reported spontaneously and in the literature. Generally the reported outcome in these cases was improvement or recovery. In the event of overdosage the patient should be observed and appropriate symptomatic treatment should be given.

Events that have been reported at different dose ranges are as follows:

Adult Overdose

1,200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash, erythema, oedema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headNRAe, decreased appetite, increased bilirubin and liver transaminase level. 1,800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain. 6,400 mg (single dose): A case report in the literature about one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.

8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

Pediatric Overdose

One 3-year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhea and anorexia and another 3-year-old male exposed to a single dose of 980 mg dose experienced decreased white blood cell count and diarrhea.

For the most recent information in the management of a suspected drug overdose, contact your regional poison centre or Health Canada's toll-free-number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 100 mg and 400 mg	Colloidal anhydrous silica, crospovidone, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol & talc.

Dosage Form

NRA-IMATINIB 100 mg: Dark yellow to brownish orange, round, biconvex, film-coated tablets, debossed with "FG" and "1" on either side of breakline on one side and plain on the other side.

NRA-IMATINIB 400 mg: Dark yellow to brownish orange, oval shaped, biconvex, film-coated tablets, debossed with "FG" and "2" on either side of breakline on one side and plain on the other side.

Packaging

All strengths are packaged in HDPE bottles containing 30 Tablets, 90 Tablets and 500 Tablets.

NRA-IMATINIB 100 mg is available in cartons containing 3, and 12 blister strips of 10 tablets.

NRA-IMATINIB 400 mg is available in cartons containing 3, and 6 blister strips of 10 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Fluid Retention and edema

Imatinib mesylate is often associated with edema and occasionally serious fluid retention (see 8.2 Clinical Trial Adverse Reactions). All Grades of fluid retention/edema were reported in up to 61.7% for newly diagnosed CML patients, up to 76.2% for other CML patients across all clinical trials, and up to 80.3% for GIST patients. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention as fluid retention can occur after months of treatment. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher imatinib dose. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking imatinib mesylate and in 2.1% to 5.8% of other adult CML patients taking imatinib mesylate. In addition, other severe fluid retention events (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) were reported in 1.3% of newly diagnosed CML patients taking imatinib mesylate and in 1.7% to 6.2% of other adult CML patients taking imatinib mesylate.

Hemorrhage

All Grades of hemorrhage were reported in up to 28.9% for newly diagnosed CML patients, up to 53% for other CML patients across all clinical trials, and up to 29.9% for GIST patients.

In the newly diagnosed CML trial, 1.8% of patients had Grades 3/4 hemorrhage. In the unresectable and/or metastatic malignant GIST clinical trial (B2222) eight patients (5.4%, five patients in the 600 mg dose group and three patients in the 400 mg dose group) were reported to have had gastrointestinal (GI) bleeds or intra-tumoral bleeds. Four patients with intra-tumoral bleeds had either intra-abdominal or intra-hepatic, depending on the anatomical location of the tumor lesions. One patient, who had a history of GI bleeding prior to the study, died due to gastrointestinal bleeding.

In addition, gastric antral vascular ectasia (GAVE), a rare cause of GI hemorrhage, has been reported in post-marketing experience in patients with CML, GIST, ALL and other diseases. Patients should therefore be monitored for gastrointestinal symptoms at the start of and during therapy with NRA-IMATINIB. When needed, NRA-IMATINIB discontinuation may be considered. Time to GAVE diagnosis was commonly reported at about 1 year of exposure but was variable (6 days to 7 years) after starting treatment with imatinib mesylate (see 8.2 Clinical Trial Adverse Reactions).

Subdural hematomas have been reported in association with imatinib administration in patients with other contributing factors, including older age (e.g., age greater than 50-55 years); thrombocytopenia due to the underlying malignancy or concomitant administration of multi-agent chemotherapy; concomitant administration of medications that increase bleeding risk; and prior lumbar puncture or head trauma. In clinical trials, the incidence of subdural hematoma has ranged from 0 to 2.4%.

This risk of bleeding should be evaluated carefully in all patients. Caution should be exercised with the concomitant use of antiplatelet agents or warfarin, especially in patients who are thrombocytopenic. Platelet counts and prothrombin time should be measured on a regular

basis when imatinib is used concurrently with anticoagulants, prostacyclins, or other medications that increase bleeding risk. Patients who experience head trauma or have unexplained neurological symptoms should be evaluated for subdural hematoma. In view of a potential interaction between imatinib mesylate and warfarin leading to increased exposure to warfarin, patients who require anticoagulation with warfarin should be monitored especially closely when NRA-IMATINIB dose adjustments are necessary (see 9.4 Drug-Drug Interactions).

Toxicities From Long-Term Use

It is important to consider potential toxicities suggested by animal studies, specifically, liver kidney and cardiac toxicity, and immunosuppression. Liver toxicity was observed in rats, dogs and cynomolgus monkeys in repeated dose studies. Most severe toxicity was noted in dogs and included elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia.

Tumour Lysis Syndrome (TLS)

Tumor lysis syndrome has occurred in patients taking imatinib mesylate, including fatal cases (see 8.5 Post-Market Adverse Reactions). Patients at increased risk for TLS include those with tumours having a high proliferative rate (e.g. CML-blast crisis), concomitant chemotherapy or radiotherapy or having a solid tumour of large size (bulky disease), decreased kidney function or elevated lactate dehydrogenase (LDH) at baseline. Preventative measures, including correction of clinically significant dehydration and treatment of high uric acid levels, should be considered for patients at increased risk of developing TLS (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests).

Carcinogenesis and Genotoxicity

A 2-year preclinical carcinogenicity study conducted in rats demonstrated renal adenomas/carcinomas, urinary bladder and urethra papillomas, papillomas/carcinomas of the preputial and clitoral gland, adenocarcinomas of the small intestine, adenomas of the parathyroid glands, benign and malignant tumors of the adrenal medulla and papillomas/carcinomas of the nonglandular stomNRA (See 16 NON-CLINICAL TOXICOLOGY - Carcinogenicity).

Long-term, non-neoplastic histological changes identified in the preclinical carcinogenicity study in rats include cardiomyopathy.

The relevance of these findings in the rat carcinogenicity study for humans is not known. An analysis of the clinical safety data from clinical trials and spontaneous adverse event reports did not provide evidence of an increased overall incidence of malignancies in patients treated with imatinib mesylate compared to that of the general population.

However, adverse events in cancer patients are significantly under reported and a large proportion of patients treated with imatinib mesylate have had limited follow-up thus not permitting a final analysis of the potential for an increased incidence of a secondary malignancy in patients treated with imatinib mesylate.

Cardiovascular

Severe congestive heart failure (CHF) and reduction of left ventricular ejection fraction (LVEF) have been reported in patients taking imatinib mesylate. Although several of these patients had pre-existing conditions including hypertension, diabetes and prior coronary artery disease, they were subsequently diagnosed with CHF. Patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully and those with symptoms or signs consistent with CHF should be evaluated and treated. In patients with history of cardiac disease or in elderly patients, a baseline evaluation of LVEF is recommended prior to initiation of NRA-IMATINIB therapy.

In patients with hypereosinophilic syndrome (HES) with occult or known infiltration of HES cells within the myocardium, isolated cases of cardiogenic shock/left ventricular dysfunction believed to be associated with HES cell degranulation upon initiation of imatinib mesylate therapy, have been reported. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib mesylate. Myelodysplastic/myeloproliferative diseases (MDS/MPD) and systemic mastocytosis (SM) might be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL and in patients with MDS/MPD or ASM and SM-AHNMD associated with high eosinophil levels. These patients with HES/CEL or ASM, SM-AHNMD and MDS/MPD must be also on 1-to 2 mg/kg of prednisone equivalent oral steroids for one to two weeks, initiated at least 2 days prior to beginning NRA-IMATINIB therapy.

Driving and Operating MNRAinery

Reports of motor vehicle accidents have been received in patients receiving imatinib mesylate. Caution should be recommended when driving a car or operating mNRAinery (see 8.5 Post-Market Adverse Reactions and 9.3 Drug-Behavioural Interactions).

Endocrine and Metabolism

Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib mesylate. Thyroid-Stimulating Hormone (TSH) levels should be closely monitored in such patients.

Gastrointestinal

Imatinib mesylate is sometimes associated with GI irritation. NRA-IMATINIB should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

See 7 WARNINGS AND PRECAUTIONS, General for more information on gastrointestinal hemorrhage.

Hematologic

Hematologic Toxicity

Treatment with imatinib mesylate is often associated with neutropenia or thrombocytopenia (see 8.4 Abnormal Laboratory Findings). Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). The occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias involving neutropenia (31%), thrombocytopenia (16%) and anemia (14%). These generally occur within the first several months of therapy (see 4.2 Recommended Dose and Dosage Adjustment - Hematologic adverse drug reactions).

An increased rate of opportunistic infections was observed in a monkey study with chronic imatinib treatment. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans, where all grades of lymphopenia were observed in 0.3% patients).

Hepatic/Biliary/Pancreatic

Liver Failure

There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some cases the outcome was fatal. One patient, who was taking acetaminophen regularly for fever along with imatinib mesylate, died of acute liver failure (see 9.4 Drug-Drug Interactions).

Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with imatinib mesylate (see 8.2 Clinical Trial Adverse Reactions). Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with NRA-IMATINIB (see 8.2 Clinical Trial Adverse Reactions and 4.2 Recommended Dose and Dosage Adjustment – Hepatic Impairment). Patients with hepatic impairment should be closely monitored. Although pharmacokinetic analysis results showed there is considerable inter-subject variation, the mean exposure to imatinib did not differ significantly between patients with mild and moderate liver dysfunction (as measured by dose normalized AUC) and patients with normal liver function. Patients with severe liver dysfunction demonstrated increased exposure to imatinib and its active metabolite CGP 74588. Liver function monitoring remains crucial as no long term toxicity and tolerability have been established (see 10.3 Pharmacokinetics – Hepatic Insufficiency).

In GIST patients with liver metastases, exposure to imatinib mesylate may be higher than in CML patients, due to impaired liver function (see 8.2 Clinical Trial Adverse Reactions).

Hepatotoxicity has been observed in patients treated with imatinib mesylate. All Grades of liver toxicity (including liver failure) were reported in up to 11.6% for newly diagnosed CML patients,

up to 12% for other CML patients across all clinical trials, and up to 12.2% for unresectable and/or metastatic malignant GIST patients.

Immune

Hepatitis B virus Reactivation

Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus after receiving a Bcr-Abl tyrosine kinase inhibitor (TKI), including imatinib mesylate. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or death.

Patients should be tested for HBV infection before initiating treatment with NRA-IMATINIB. Patients currently on NRA-IMATINIB should have baseline testing for HBV infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with NRA-IMATINIB should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Monitoring and Laboratory Tests

Patients with known cardiac disease or risk factors for cardiac failure should be monitored carefully and those with symptoms or signs consistent with CHF should be evaluated and treated. In patients with history of cardiac disease or in elderly patients, a baseline evaluation of LVEF is recommended prior to initiation of NRA-IMATINIB therapy (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

For patients receiving NRA-IMATINIB, complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months) (see 7 WARNINGS AND PRECAUTIONS - Hematologic and 4.2 Recommended Dose and Dosage Adjustment – Hematologic adverse drug reactions).

Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated (see 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic and 4.2 Recommended Dose and Dosage Adjustment – Hepatic Impairment).

Patients should be weighed and monitored regularly for signs and symptoms of fluid retention as fluid retention can occur after months of treatment with NRA-IMATINIB (see 7 WARNINGS AND PRECAUTIONS - General).

Thyroid-Stimulating Hormone (TSH) levels should be closely monitored in thyroidectomy patients undergoing levothyroxine replacement during treatment with NRA-IMATINIB (see 7 WARNINGS AND PRECAUTIONS – Endocrine and Metabolism).

Signs and symptoms consistent with tumour lysis syndrome (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, elevated LDH, high fevers) should be monitored at baseline and during initial treatment with NRA-IMATINIB (see 7 WARNINGS AND PRECAUTIONS - General and 4.1 Dosing Considerations – Tumour Lysis Syndrome (TLS)).

Close monitoring of growth in children under NRA-IMATINIB treatment is highly recommended (see 7.1.3 Pediatrics).

During treatment with NRA-IMATINIB serum electrolytes should be regularly monitored for possible hypophosphatemia, hyperkalemia, and hyponatremia in all patients as well as glucose, blood urea nitrogen (BUN) and creatinine. In addition, in pediatric patients, serum calcium and albumin should also be regularly monitored. Grades 3/4 hypophosphatemia have been observed in 16.5% (15% Grade 3 and 1.5% Grade 4) of patients in a phase I dose finding study 03001 (N=143) and a phase II study 0102 (N=260) of chronic myeloid leukemia in blast crisis.

In patients with CML, regular response monitoring, particularly when therapy is modified, is essential to detect early signs of loss of response so that appropriate actions can be taken to avoid disease progression. A loss of response can occur at any time, but is more likely when imatinib treatment is modified (see 4.2 Recommended Dose and Dosage Adjustment – Chronic myeloid leukemia (CML)).

Females of reproductive potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml within 1 week prior to beginning therapy (see 7.1.1 Pregnancy – Female Patients of Reproductive Potential).

Musculoskeletal

Cases of osteonecrosis have been uncommonly reported in adult and pediatric patients treated with imatinib mesylate, including serious cases requiring treatment discontinuation, and/or surgical interventions. The femur head was the most commonly affected site; less commonly affected sites included the tibia, femur shaft, jaw, finger, and calcaneus (see 8.5 Post-Market Adverse Reactions).

Renal

Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals.

Imatinib mesylate and its metabolites are not excreted via the kidney to a significant extent. Creatinine clearance (CrCL) is known to decrease with age, and age did not significantly affect imatinib kinetics.

In patients with impaired renal function, imatinib mesylate plasma exposure is higher (1.5- to 2-fold increase) than in patients with normal renal function, probably due to an elevated plasma level of alpha-acid glycoprotein (AGP), an imatinib mesylate-binding protein, in patients with renal dysfunction. As well, there is a significant correlation in the incidence of serious adverse

events with decreased renal function (p=0.0096). Patients with mild or moderate renal impairment should be treated with caution (see 4.2 Recommended Dose and Dosage Adjustment – Renal Impairment). Since the effect of imatinib mesylate treatment on patients with severe renal dysfunction or on dialysis has not been sufficiently assessed, recommendations on the treatment of these patients with NRA-IMATINIB cannot be made. Patients with history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with renal failure should be evaluated and treated.

Long term treatment with NRA-IMATINIB may result in declines in renal function. Patients treated with imatinib in clinical studies had a decrease over time in estimated glomerular filtration rate (eGFR). Treatment-naive patients with newly-diagnosed CML initiated on imatinib among three Phase III trials showed a decline in eGFR from a median baseline value of 100.1 ml/min/1.73m^2 (N=1279) to 93.5 ml/min/1.73m^2 at 6 months (N=1213), 92.8 ml/min/1.73m^2 at 1 year (N=1161) and 85.5 ml/min/1.73m^2 at 5 years (N=585). Monitoring for renal function should be undertaken before initiating therapy and periodically thereafter.

Reproductive Health

Fertility

Stem cell factor and c-Kit genes are known to be important for germ cell development. Human studies on male patients receiving imatinib mesylate and its effect on male fertility and spermatogenesis have not been performed. However, clinical evidence of profound oligospermia with imatinib mesylate use has been reported in the literature as has clinical evidence for maintained male fertility. There is also pre-clinical evidence of impaired spermatogenesis, lower testes and epididymal weights as well as a reduced number of motile sperm without a reduction in fertility (see 16 NON-CLINICAL TOXICOLOGY - Reproductive and Developmental Toxicology). Therefore, physicians should advise and counsel their male patients as appropriate.

Respiratory

Pulmonary Events

Rare cases of pulmonary fibrosis and interstitial pneumonitis have been reported in patients who have received imatinib mesylate. However, no definitive relationship has been established between the occurrence of these pulmonary events and treatment with imatinib mesylate.

Skin

Skin and Mucosa

Although rare, Erythema multiforme (EM), Toxic epidermal Necrolysis (TEN) and Stevens Johnson syndrome (SJS) have been reported in patients who have received imatinib mesylate. Skin biopsies in some cases of exfoliative skin rash associated with imatinib mesylate use have

shown a mixed cellular infiltrate characteristic of a toxic drug reaction. Severe cases of exfoliative rash may require treatment interruption or discontinuation.

Drug reaction with eosinophilia and systemic symptoms (DRESS), a potentially life-threatening syndrome including fever, severe skin eruption, lymphadenopathy, hematologic abnormalities (eosinophilia or atypical lymphocytes), and internal organ involvement, has also been reported in imatinib mesylate-treated patients. DRESS regressed when imatinib mesylate was discontinued, and in all cases where the drug was re-introduced, DRESS recurred. If DRESS occurs, NRA-IMATINIB should be interrupted, and permanent discontinuation should be considered.

7.1 Special Populations

7.1.1 Pregnancy

NRA-IMATINIB should not be administered to pregnant women.

NRA-IMATINIB can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies on the use of imatinib mesylate in pregnant women.

Patients should advise their physician if they are pregnant. If it is used during pregnancy the patient should be apprised of the potential risk to the fetus.

Females of reproductive potential should be advised to use effective birth control (methods that result in less than 1 % pregnancy rates) when using NRA-IMATINIB during treatment and for at least 15 days after stopping treatment with NRA-IMATINIB.

Females of reproductive potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/ml within 1 week prior to initiating NRA-IMATINIB.

Teratogenicity and significant post-implantation loss have been observed in rat studies (see 16 NON-CLINICAL TOXICOLOGY - Reproductive and Developmental Toxicology). There have been post-marketing reports of spontaneous abortions and infant congenital anomalies from women who have taken imatinib mesylate.

7.1.2 Breastfeeding

Imatinib and its active metabolite can be excreted into breast milk in humans and in animals. There are cases of imatinib exposure during lactation in humans including one case reported the milk: plasma ratio of 0.5 for imatinib and 0.9 for the metabolite. Since the effects of exposure of the infant to imatinib are potentially serious, women should not breast feed during treatment and for at least 15 days after stopping treatment with NRA-IMATINIB.

7.1.3 Pediatrics

Pediatrics (<18 years of age): There is no experience with the use of imatinib mesylate in pediatric patients with CML under 2 years of age. There is very limited to no experience with

the use of imatinib mesylate in pediatric patients in other indications.

There have been case reports of growth retardation in children and pre-adolescents receiving imatinib mesylate. No prospective studies have been carried out in this regard and the long term effects of prolonged treatment with imatinib mesylate on growth in pediatric patients are unknown. In a juvenile toxicology study, an impact on growth and a delay in sexual maturation were observed in rats (see 16 NON-CLINICAL TOXICOLOGY - Juvenile Toxicology). Therefore, close monitoring of growth in children under NRA-IMATINIB treatment is highly recommended.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): In the CML phase II studies, approximately 20% of patients were older than 65 years. The efficacy of imatinib mesylate was similar in all age groups studied.

In the adjuvant GIST study, 221 patients (31%) were older than 65 years. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients. The efficacy of imatinib mesylate was similar in patients older than 65 years and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Imatinib mesylate was generally well tolerated across all studies in CML and GIST. Complications of advanced malignancies and co-administered medications make causality of adverse events difficult to assess in single arm studies. The majority of imatinib mesylate-treated patients experienced adverse events at some time.

Recent published literature revealed cases of musculoskeletal pain symptoms occurring upon imatinib discontinuation following long-term treatment, with a high frequency of 18% to 46% in CML patients. Those events may persist for months and were referred to as imatinib withdrawal symptoms (IWS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Chronic Myeloid Leukemia

Imatinib mesylate was generally well tolerated with chronic oral daily dosing in patients with CML including pediatric patients. The majority of patients experienced adverse events at some point in time, however, most events were of mild to moderate Grade. In adult clinical trials, drug discontinuation for drug-related adverse events was observed in 2.4% of newly diagnosed

patients, in 5 % of patients in chronic phase, 8% in accelerated phase and 9% in blast crisis.

The most frequently reported drug-related adverse events were fluid retention (superficial edema and other fluid retention events), nausea, vomiting, diarrhea, muscle cramps, fatigue and rash (Refer to Table 3 and 4 for newly diagnosed CML and other CML patients, respectively). Superficial edemas were a common finding in all studies described primarily as periorbital edemas or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib mesylate (see 4.2 Recommended Dose and Dosage Adjustment – Chronic myeloid leukemia (CML)).

Other adverse events such as pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema may be collectively described as "other fluid retention events". These events were usually managed by withholding imatinib mesylate treatment temporarily and/or with diuretics and/or other appropriate supportive care measures. However, a few of these events may be serious or life threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure. The following tables list the adverse experiences which occurred in ≥ 10% of patients in the clinical trials, regardless of relationship to therapy.

Table 3 Adverse experiences Regardless of Relationship to Study Drug reported in newly diagnosed CML (≥10% of all patients)[1]

Adverse event (preferred term)	All Grades		CTC Grades 3/4	
	Imatinib Mesylate N=551 (%)	IFN+Ara-C N=533 (%)	Imatinib Mesylate N=551 (%)	IFN+Ara-C N=533 (%)
Any event	**99.1**	**99.6**	**57.2**	**77.3**
Gastrointestinal disorders				
Nausea	49.5	61.5	1.3	5.1
Diarrhea	45.4	43.3	3.3	3.2
Abdominal pain	36.5	25.9	4.2	3.9
Vomiting	22.5	27.8	2.0	3.4
Dyspepsia	18.9	8.3	0	0.8
Constipation	11.4	14.4	0.7	0.2
Dry mouth	2.9	10.9	0	0.2
General disorders and administration site conditions				
Fluid retention	61.7	11.1	2.5	0.9
- Superficial edema	59.9	9.6	1.5	0.4
- Other fluid retention events	6.9	1.9	1.3	0.6
Fatigue	38.8	67.0	1.8	25.1
Pyrexia	17.8	42.6	0.9	3.0
Rigors	9.3	34.0	0.2	0.8
Asthenia	8.0	16.9	0.2	3.8
Influenza like illness	7.3	15.9	0	0.9
Mucosal inflammation	1.1	10.3	0	3.2

Adverse event (preferred term)	All Grades		CTC Grades 3/4	
	Imatinib Mesylate N=551 (%)	IFN+Ara-C N=533 (%)	Imatinib Mesylate N=551 (%)	IFN+Ara-C N=533 (%)
Hepatobiliary disorders				
Liver toxicity (including liver failure)	11.6	17.3	4.0	5.1
Infections and infestations				
Nasopharyngitis	30.5	8.8	0	0.4
Upper respiratory tract infection	21.2	8.4	0.2	0.4
Influenza	13.8	6.2	0.2	0.2
Sinusitis	11.4	6.0	0.2	0.2
Investigations				
Weight increased	15.6	2.6	2.0	0.4
Weight decreased	5.1	17.3	0.4	1.3
Metabolic and nutritional disorders				
Anorexia	7.1	31.7	0	2.4
Musculoskeletal & connective tissue disorders				
Muscle cramps	49.2	11.8	2.2	0.2
Musculoskeletal pain	47.0	44.8	5.4	8.6
Joint pain	31.4	38.1	2.5	7.7
Myalgia	24.1	38.8	1.5	8.3
Bone pain	11.3	15.6	1.6	3.4
Nervous system disorders				
HeadNRAe	37.0	43.3	0.5	3.8
Dizziness	19.4	24.4	0.9	3.8
Psychiatric disorders				
Depression	14.9	35.8	0.5	13.1
Insomnia	14.7	18.6	0	2.3
Anxiety	9.6	11.8	0.5	2.6
Respiratory disorders				
Cough	20.0	23.1	0.2	0.6
Pharyngolaryngeal pain	18.1	11.4	0.2	0
Dyspnea	9.3	14.4	1.8	1.7
Skin and subcutaneous disorders				
Rash and related terms	40.1	26.1	2.9	2.4
Night sweats	9.8	15.8	0.2	0.4
Pruritus	9.8	11.8	0.2	0.2
Sweating increased	5.8	14.8	0.2	0.4
Alopecia	4.9	22.3	0	0.6
Vascular disorders				
Hemorrhage	28.9	21.2	1.8	1.7
- GI hemorrhages	1.6	1.1	0.5	0.2
- CNS hemorrhages	0.2	0.4	0	0.4

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

Table 4 Adverse Experiences Regardless of Relationship to Study Drug Reported in Other CML Clinical Trials (≥10% of All patients in any trial) [1]

System Affected	Myeloid blast crisis N=260 (%)		Accelerated phase N=235 (%)		Chronic phase IFN failure N=532(%)	
	All Grades	CTC Grades 3/4	All Grades	CTC Grades 3/4	All Grades	CTC Grades 3/4
Gastrointestinal disorders						
Nausea	71	5	73	5	63	3
Vomiting	54	4	58	3	36	2
Diarrhea	43	4	57	5	48	3
Abdominal pain¥	30	6	33	4	32	1
Constipation	16	2	16	0.9	9	0.4
Dyspepsia	12	0	22	0	27	0
General disorders and administration site conditions						
Fluid retention¥	72	11	76	6	69	4
- Superficial edemas¥	66	6	74	3	67	2
- Other fluid retention events[2] ¥	22	6	15	4	7	2
Pyrexia	41	7	41	8	21	2
Fatigue	30	4	46	4	48	1
Asthenia	18	5	21	5	15	0.2
Rigors	10	0	12	0.4	10	0
Chest pain	7	2	10	0.4	11	0.8
Hepatobiliary disorders						
Liver toxicity (including liver failure)	10	5	12	6	6	3
Infections and infestations						
Nasopharyngitis	10	0	17	0	22	0.2
Pneumonia NOS	13	7	10	7	4	1
Upper respiratory tract infection NOS	3	0	12	0.4	19	0
Sinusitis NOS	4	0.4	11	0.4	9	0.4
Influenza	0.8	0.4	6	0	11	0.2
Investigations						
Weight increase	5	1	17	5	32	7
Metabolic and nutritional disorders						
Anorexia	14	2	17	2	7	0
Hypokalemia	13	4	9	2	6	0.8
Musculoskeletal & connective tissue disorders						
Musculoskeletal pain¥	42	9	49	9	38	2
Muscle cramps¥	28	1	47	0.4	62	2
Joint pain (Arthralgia) ¥	25	5	34	6	40	1
Myalgia	9	0	24	2	27	0.2
Nervous system disorders						

System Affected	Myeloid blast crisis N=260 (%)		Accelerated phase N=235 (%)		Chronic phase IFN failure N=532(%)	
	All Grades	CTC Grades 3/4	All Grades	CTC Grades 3/4	All Grades	CTC Grades 3/4
HeadNRAe	27	5	32	2	36	0.6
Dizziness	12	0.4	13	0	16	0.2
Psychiatric disorders						
Insomnia	10	0	14	0	14	0.2
Anxiety	8	0.8	12	0	8	0.4
Respiratory disorders						
Dyspnea NOS	15	4	21	7	12	0.9
Cough	14	0.8	27	0.9	20	0
Pharyngitis	10	0	12	0	15	0
Skin and subcutaneous disorders						
Rash and related terms[¥]	36	5	47	5	47	3
Night sweats	13	0.8	17	1	14	0.2
Pruritis	8	1	14	0.9	14	0.8
Vascular disorders						
Hemorrhages [¥]	53	19	49	11	30	2
- CNS hemorrhages[¥]	9	7	3	3	2	1
- GI hemorrhages[¥]	8	4	6	5	2	0.4

[¥]**Grouped events**

(1) All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment

(2) Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

Acute Lymphoblastic Leukemia

The adverse reactions were similar for Ph+ ALL as for CML. The most frequently reported non-hematologic drug-related adverse events were fluid retention (superficial edema and other fluid retention events), nausea, vomiting, diarrhea, muscle cramps, fatigue and rash. Superficial edemas were a common finding in all studies described primarily as periorbital edemas or lower limb edemas. However, these edemas were rarely severe and may be managed with diuretics, other supportive measures, or by reducing the dose of imatinib mesylate (see 4.2 Recommended Dose and Dosage Adjustment – Ph+ Acute Lymphoblastic Leukemia (Ph+ALL)).

Myelodysplastic/Myeloproliferative Diseases

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with imatinib mesylate for MDS/MPD in Trial B2225, are shown in Table 5.

Table 5 Adverse Experiences Regardless of Relationship to Study Drug Reported (more than one patient) in MDS/MPD Patients in Trial B2225 (≥10% all patients) all Grades

Preferred term	N=7 n (%)
Nausea	4 (57.1)
Diarrhea	3 (42.9)
Anemia	2 (28.6)
Fatigue	2 (28.6)

Muscle cramp	3 (42.9)
Arthralgia	2 (28.6)
Periorbital edema	2 (28.6)

Aggressive sub-types of Systemic Mastocytosis (ASM and SM-AHNMD)

All ASM patients experienced at least one adverse event at some time. The most frequently reported adverse events were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritis, rash and lower respiratory tract infection. None of the 5 patients in Study B2225 with ASM discontinued imatinib mesylate due to drug-related adverse events or abnormal laboratory values.

Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The overall safety profile in this HES/CEL small patient population does not seem different from the known safety profile of imatinib mesylate observed in other larger populations of hematologic malignancies, such as CML. However, in patients with HES and cardiac involvement, isolated cases of cardiogenic shock/left ventricular dysfunction have been associated with the initiation of imatinib mesylate therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding imatinib mesylate (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular). All patients experienced at least one adverse event, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematologic abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia and anemia.

Dermatofibrosarcoma Protuberans

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with imatinib mesylate for DFSP in Trial B2225 are shown in Table 6.

Table 6 Adverse Experiences Regardless of Relationship to Study Drug Reported in DFSP Patients in Trial B2225 (≥10% all patients) all Grades

Preferred term	N=12 n (%)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Vomiting	3 (25.0)
Periorbital edema	4 (33.3)
Face edema	2 (16.7)
Rash	3 (25.0)
Fatigue	5 (41.7)
Edema peripheral	4 (33.3)
Pyrexia	2 (16.7)
Eye edema	4 (33.3)
Lacrimation increased	3 (25.0)
Dyspnea exertional	2 (16.7)
Anemia	3 (25.0)

Rhinitis	2 (16.7)
Anorexia	2 (16.7)

Gastrointestinal Stromal Tumors

Unresectable and/or Metastatic Malignant GIST

Imatinib mesylate was generally well tolerated in patients with unresectable and/or metastatic malignant GIST. Most events were of mild to moderate severity. Drug was discontinued for adverse events in 7 (4.7%) patients in both treatment groups. The most frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue and rash.

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with imatinib mesylate are shown in Table 7. No major differences were seen in the incidence or severity of adverse events between the 400 mg or 600 mg dose groups.

Table 7 Adverse Experiences Regardless of Relationship to Study Drug Reported in the Unresectable and/or Metastatic Malignant GIST (B2222) trial (≥10%) of all patients[1]

	All doses (n=147) 600 mg n=73	
	All Grades (%)	Grades 3/4 (%)
Preferred Term		
Blood and lymphatic system disorders		
Anemia	19.7	5.4
Eye disorders		
Lacrimation increased	17.0	0
Gastrointestinal disorders		
Nausea	68.7	4.8
Diarrhea	64.6	4.8
Abdominal pain	57.1	8.8
Vomiting	36.7	4.1
Flatulence	32.0	0
Dyspepsia	15.0	0
Constipation	10.2	0.7
General disorders and administration site		
Any Fluid retention	80.3	9.5
Superficial edema	78.9	5.4
Other fluid retention events [2]	13.6	5.4
Fatigue	50.3	1.4
Pyrexia	20.4	1.4
Other hemorrhage	24.5	2.7
Hepatobiliary disorders		
Liver Toxicity	12.2	6.8
Infections and infestations		
Nasopharyngitis	23.8	0

Upper Respiratory Tract Infection	15.6	0
Musculoskeletal. & connective tissue disorders		
Muscle cramps	52.4	0
Musculoskeletal pain	33.3	3.4
Back pain	24.5	0
Join Pain	12.9	0.7
Nervous system disorders		
HeadNRAe	36.1	0
Dizziness	11.6	0
Peaces abnormal		
Loose Stools	10.9	0
Psychiatric disorders		
Insomnia	18.4	0.7
Anxiety	8.8	0
Respiratory disorders		
Pharyngolaryngeal Pain	9.5	0
Skin and subcutaneous disorders		
Rash and related terms	45.6	3.4
Surgical and medical procedures		
Operation	10.2	4.8
Vascular disorders		
Any Hemorrhage	29.9	8.2
Upper G-I tract bleeding/perforation	4.1	3.4
Tumor Hemorrhage	2.7	2.7

(1) All adverse events occurring in ³10% of patients are listed regardless of suspected relationship to treatment.
(2) Other fluid retention events included pleural effusion and ascites.

Adjuvant Treatment of GIST

The majority of both imatinib mesylate and placebo treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting and abdominal pain. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations including patients with unresectable and/or malignant metastatic GIST. Drug was discontinued for adverse reactions in 57 patients (17%) and 11 patients (3%) of the imatinib mesylate and placebo treated patients respectively. Edema, gastrointestinal disturbances (nausea, vomiting, abdominal distension and diarrhea), fatigue, low hemoglobin and rash were the most frequently reported adverse reactions at the time of discontinuation.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with imatinib mesylate are shown in Table 8.

Table 8 Adverse Reactions Regardless of Relationship to Study Drug Reported in the Adjuvant GIST Trial (≥5% of imatinib mesylate Treated Patients)

	All CTC Grades		CTC Grade 3 and above	
	Imatinib mesylate (n=337)	Placebo (n=345)	Imatinib mesylate (n=337)	Placebo (n=345)
Preferred Term	**%**	**%**	**%**	**%**
Blood and lymphatic system disorders				
Leukopenia	5.0	2.6	0.3	0
Eye disorders				
Lacrimation Increased	9.8	3.8	0	0
Vision Blurred	5.0	2.3	0	0
Gastrointestinal disorders				
Diarrhea	59.3	29.3	3.0	1.4
Nausea	53.1	27.8	2.4	1.2
Vomiting	25.5	13.9	2.4	0.6
Abdominal Pain	21.1	22.3	3.0	1.4
Dyspepsia	17.2	13.0	0.9	0
Constipation	12.8	17.7	0	0.3
Abdominal Distension	7.4	6.4	0.3	0.3
Flatulence	8.9	9.6	0	0
Abdominal Pain Upper	6.2	6.4	0.3	0
Stomatitis	5.0	1.7	0.6	0
General disorders and administration site conditions				
Fatigue	57.0	40.9	2.1	1.2
Peripheral Edema	26.7	14.8	0.3	0
Facial Edema	6.8	1.2	0.3	0
Hepatobiliary disorders				
Liver enzymes (ALT) Increased	16.6	13.0	2.7	0
Liver Enzymes (AST) Increased	12.2	7.5	2.1	0
Investigations				
Hemoglobin Decreased	46.9	27.0	0.6	0
Weight Increased	16.9	11.6	0.3	0
Neutrophil Count Decreased	16.0	6.1	3.3	0.9
White Blood Cell Count Decreased	14.5	4.3	0.6	0.3
Blood Creatinine Increased	11.6	5.8	0	0.3
Weight Decreased	10.1	5.2	0	0
Blood Alkaline Phosphatase Increased	6.5	7.5	0	0
Platelet Count Decreased	5.0	3.5	0	0
Metabolic and nutritional disorders				
Anorexia	16.9	8.7	0.3	0
Hyperglycemia	9.8	11.3	0.6	1.7
Hypokalemia	7.1	2.0	0.9	0.6
Hypocalcemia	5.6	1.7	0.3	0

	All CTC Grades		CTC Grade 3 and above	
	Imatinib mesylate (n=337)	Placebo (n=345)	Imatinib mesylate (n=337)	Placebo (n=345)
Preferred Term	**%**	**%**	**%**	**%**
Musculoskeletal & connective tissue disorders				
Muscle spasms	16.3	3.3	0	0
Myalgia	12.2	11.6	0	0.3
Arthralgia	15.1	14.5	0	0.3
Back Pain	7.4	8.1	0.6	0
Pain in Extremity	7.4	7.2	0.3	0
Nervous system disorders				
HeadNRAe	19.3	20.3	0.6	0
Dizziness	12.5	10.7	0	0.3
Insomnia	9.8	7.2	0.9	0
Depression	6.8	6.4	0.9	0.6
Dysgeusia	6.5	2.9	0	0
Neuropathy Peripheral	5.9	6.4	0	0
Respiratory disorders				
Cough	11.0	11.3	0	0
Upper Respiratory Tract Infection	5.0	3.5	0	0
Skin and subcutaneous disorders				
Periorbital Edema	47.2	14.5	1.2	0
Rash (Exfoliative)	26.1	12.8	2.7	0
Pruritus	11.0	7.8	0.9	0
Alopecia	9.5	6.7	0	0
Rash	8.9	5.2	0.9	0
Dry skin	6.5	5.2	0	0

[1]All adverse reactions occurring in ≥5% of patients are listed regardless of suspected relationship to treatment.
A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.

Adverse Drug Reactions in clinical studies for CML and Unresectable and/or Metastatic Malignant GIST

The following adverse reactions as applicable are ranked under headings of frequency, the most frequent first, using the following convention: *Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000), including isolated reports*. Adverse reactions reported below are based on the registration studies for CML and GIST. Frequencies are determined by reported related events according to the investigator.

Cardiovascular

Common: flushing[1]

Uncommon: palpitations, cardiac failure congestive (on a patient-year basis, cardiac events including congestive heart failure were more commonly observed in patients with transformed CML than in patients with chronic CML), pulmonary edema, tNRAycardia, hypertension[1], hematoma[1], hypotension[1], peripheral coldness[1], Raynaud's phenomenon[1]

Rare: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion

Clinical laboratory tests (See Tables 9, 10 and 12)

Uncommon: blood CPK increased, blood LDH increased

Rare: blood amylase increased

Dermatologic

Common: pruritus, face edema, dry skin, erythema, alopecia, photosensitivity reaction

Uncommon: rash pustular, sweating increased, urticaria, increased tendency to bruise, exfoliative dermatitis, onychoclasis, folliculitis, petechie, psoriasis, bullous eruption, nail disorder, skin pigmentation changes, purpura, palmar-plantar erythrodysaesthesia syndrome

Rare: nail discolouration, vesicular rash, erythema multiforme, leukocytoclastic vasculitis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), acute febrile neutrophilic dermatosis (Sweet's syndrome)

Digestive

Common: flatulence, abdominal distension, gastroesophageal reflux, dry mouth, gastritis

Uncommon: stomatitis, mouth ulceration, eructation, malaena, oesophagitis, ascites, gastric ulcer, hematemesis, cheilitis, dysphagia, pancreatitis

Rare: colitis, ileus, inflammatory bowel disease.

General Disorders and Administration Site Conditions

Common: weakness, anasarca, chills, rigors

Uncommon: chest pain, malaise

Hematologic (See Tables10, 11 and 13)

Common: pancytopenia, febrile neutropenia

Uncommon: thrombocythemia, lymphopenia, eosinophilia, lymphadenopathy

Rare: aplastic anemia, hemolytic anemia

Hepatobiliary disorders

Uncommon: jaundice, hepatitis, hyperbilirubinemia

Rare: hepatic failure, hepatic necrosis (some fatal cases of hepatic necrosis have been reported)

Hypersensitivity

Rare: angioedema

Infections

Uncommon: sepsis, herpes simplex, herpes zoster, sinusitis, cellulitis, influenza, urinary tract infection, gastroenteritis

Rare: fungal infection

Metabolic and nutritional

Common: anorexia, weight decreased

Uncommon: hypophosphatemia, dehydration, gout, appetite disturbances, hyperuricemia, hypercalcemia, hyperglycemia, hyponatremia

Rare: hyperkalemia, hypomagnesemia

Musculoskeletal

Common: joint swelling

Uncommon: joint and muscle stiffness

Rare: muscular weakness, arthritis

Nervous system/psychiatric

Common: paresthesia, taste disturbance, hypoesthesia

Uncommon: depression[2], libido decrease, syncope, peripheral neuropathy, somnolence, migraine, memory impairment, sciatica, restless leg syndrome, tremor

Rare: increased intracranial pressure, confusion, convulsions, optic neuritis

Neoplasm benign, malignant and unspecified (including cysts and polyps)

Uncommon: Tumor lysis syndrome

Renal

Uncommon: renal pain, renal failure acute, urinary frequency increased, hematuria

Reproductive

Uncommon: erectile dysfunction, breast enlargement, menorrhagia, menstruation irregular, sexual dysfunction, nipple pain, scrotal edema

Respiratory

Common: dyspnea, epistaxis, cough

Uncommon: pleural effusion (pleural effusion was reported more commonly in patients with GIST and in patients with transformed CML (CML-AP and CML-BC) than in patients with chronic CML), pharyngolaryngeal pain, pharyngitis

Rare: pleuritic pain, pulmonary fibrosis, pulmonary hypertension, pulmonary

hemorrhage

Special senses

Common: eyelid edema, lacrimation increased, conjunctival hemorrhage, conjunctivitis, dry eye, vision blurred

Uncommon: eye irritation, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema, vertigo, tinnitus, hearing loss

Rare: cataract, papilledema, glaucoma

[1] Vascular disorders (flushing was most common in GIST patients and hematoma was most common in patients with GIST and transformed CML (CML-AP and CML-BC)).

[2] Depression may lead to suicide ideation and/or suicide attempts.

Second malignancies in imatinib mesylate-treated patients:

Table 9 Observed and expected numbers of cases of second malignancies (excluding non-melanoma skin cancer) in clinical trials

Cancer type	Person-years	Number of cases Observed	Expected[1]	SIR (95% CI)
Cancer any type	10,967.03	79	91.16	0.87 (0.69-1.08)
Prostate	6,106.54	16	18.70	0.86 (0.49-1.39)
Kidney	10,769.60	3	2.26	1.33 (0.27-3.88)
Urinary bladder	10,766.46	2	3.72	0.54 (0.06-1.94)

[1] Expected in the general population
SIR: Standardized incidence ratio

The numbers of cancers reported in the clinical trials were similar to those expected in the general population. The observed numbers of cases for all cancers, prostate cancer and urinary bladder cancer were slightly lower than those expected in the general population, while the number of observed kidney cancer cases was slightly higher (3 compared to 2.26 expected cases respectively). In all cases, the differences were not statistically significant.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The overall safety profile of imatinib mesylate treatment in 93 pediatric patients was similar to that observed in studies with adult patients. Nausea, vomiting were the most commonly reported individual adverse events with an incidence similar to that seen in adult patients. Although most patients experienced adverse events at some time during the studies, the incidence of Grade 3/4 adverse events was low.

Significantly higher frequencies of hypocalcemia (23.5 vs 1.1%), hyperglycemia (19.6 vs 2.9%), hypoglycemia (21.6 vs 1.5%), hypophosphatemia (19.6 vs 3.3%), hypoalbuminemia (13.7 vs

0.2%) and hyponatremia (13.7 vs 0.2%) were observed in pediatric patients compared to adult patients.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Laboratory test abnormalities in CML clinical trials

Cytopenias, and particularly neutropenia and thrombocytopenia, have been a consistent finding in all studies, with the suggestion of a higher frequency at doses ≥ 750 mg (phase I study). However, the occurrence of cytopenias was also clearly dependent on the stage of the disease.

In patients with newly diagnosed CML, cytopenias were less frequent than in other CML patients (Tables 10 and 11). The frequency of Grade 3 or 4 neutropenia (ANC <1.0x10^9/L) and thrombocytopenia (platelet count <50x10^9/L) were higher in blast crisis and accelerated phase (36-48% and 32-33% for neutropenia and thrombocytopenia, respectively, Table 11) as compared to chronic phase CML (27% neutropenia and 21% thrombocytopenia). In chronic phase CML a Grade 4 neutropenia (ANC <0.5x10^9/L) and thrombocytopenia (platelet count <10x10^9/L) were observed in 9% and <1% of patients, respectively. The median duration of the neutropenic and thrombocytopenic episodes ranged usually from 2 to 3 weeks and from 3 to 4 weeks, respectively. These events can usually be managed with either a reduction of the dose or an interruption of treatment with imatinib mesylate, but can, in rare cases, lead to permanent discontinuation of treatment (see 7 WARNINGS AND PRECAUTIONS - Hematologic Toxicity).

Severe elevation of transaminases or bilirubin has been seen in <5% CML patients and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1.0% of CML patients. There have been cases of hepatic necrosis and cholestatic hepatitis and hepatic failure; in some of which outcome was fatal (see 9 DRUG INTERACTIONS).

Table 10 Newly occurring Grades 3/4 biochemical toxicities in newly diagnosed CML patients

Parameter	Imatinib Mesylate n=551 %		IFN + Ara-C n=533 %	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic				
Leucopenia	9.3	0.5	12.9	0.8
Neutropenia*	13.1	3.6	20.8	4.5
Thrombocytopenia*	8.5	0.4	15.9	0.6
Anemia	3.3	1.1	4.1	0.2
Biochemistry				
Elevated creatinine	0	0	0.4	0

Elevated bilirubin	0.9	0.2	0.2	0
Elevated alkaline phosphatase	0.2	0	0.8	0
Elevated SGOT (AST)/ SGPT (ALT)	4.7	0.5	7.1	0.4

*p<0.001 (Difference in Grade 3 + Grade 4 abnormalities between the two treatment groups).

Table 11 Laboratory test abnormalities in other CML clinical trials

	Myeloid blast crisis n= 260 (%)		Accelerated phase n=235 (%)		Chronic phase, IFN failure n=532 (%)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology parameters						
Neutropenia	16	48	23	36	27	9
Thrombocytopenia	30	33	32	13	21	<1
Anemia	42	11	34	7	6	1
Biochemistry parameters						
Elevated creatinine	1.5	0	1.3	0	0.2	0
Elevated bilirubin	3.8	0	2.1	0	0.6	0
Elevated alkaline phosphatase	4.6	0	5.5	0.4	0.2	0
Elevated SGOT (AST)	1.9	0	3	0	2.3	0
Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

CTC grades: neutropenia (grade 3≥0.5 - 1.0 x 109/L), grade 4 <0.5 x 109/L), thrombocytopenia (grade 3 ≥10 - 50 x 109/L, grade 4 <10 x 109/L), anemia (hemoglobin ≥65 - 80 g/L, grade 4<65 g/L), elevated creatinine (grade 3 >3-6 x upper limit normal range (ULN), grade 4 >6 x ULN), elevated bilirubin (grade 3 >3-10 x ULN, grade 4 >10 x ULN), elevated alkaline phosphatase (grade 3 >5-20 x ULN, grade 4 >20 x ULN), elevated SGOT or SGPT (grade 3 >5-20 x ULN, grade 4 >20 x ULN).

Clinically relevant or severe abnormalities of the 12 patients treated with imatinib mesylate for DFSP in Trial B2225 are presented in Table 12.

Table 12 Laboratory Abnormalities Reported in DFSP Patients in Trial B2225

	N=12	
CTC Grades	**Grade 3**	**Grade 4**
Hematology Parameters		
- Anemia	17%	0%
- Thrombocytopenia	17%	0%
- Neutropenia	0%	8%
Biochemistry Parameters		
- Elevated Creatinine	0%	8%

CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 10^9/L, Grade 4<0.5 x 10^9/L), thrombocytopenia (Grade 3 ≥10-50 x 10^9/L, Grade 4<10 x 10^9/L), anemia (Grade 3≥65-80 g/L, Grade 4<65 g/L), elevated creatinine (Grade 3>3-6 x upper limit normal range [ULN], Grade 4>6 x ULN).

In unresectable and/or metastatic malignant GIST patients (study B2222), 6.8% Grade 3 or 4

SGPT (serum glutamic pyruvic transferase) elevations and 4.8% Grade 3 or 4 SGOT (serum glutamic oxaloacetic transferase) elevations were observed. Bilirubin elevation was below 3%.

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values were rare (Table 13).

Table 13 Laboratory Abnormalities in the Unresectable and/or Metastatic Malignant GIST B2222 Trial

Parameter	All doses (n=147) 400 mg n=73 600 mg n=74n (%)		
	Baseline †	**New or Worsening Highest CTC Grade During Treatment**	
CTC Grading	**All Grades (1-4)**	**Grade 3**	**Grade 4**
Hematology parameters			
Anemia	70 (47.6)	8 (5.4)	1 (0.7)
Thrombocytopenia	7 (4.8)	1 (0.7)	0
Neutropenia	10 (6.8)	11 (7.5)	4 (2.7)
Biochemistry parameters			
Elevated creatinine	8 (5.4)	2 (1.4)	0
Reduced albumin	60 (40.8)	5 (3.4)	0
Elevated bilirubin	5 (3.4)	2 (1.4)	2 (1.4)
Elevated alkaline phosphatase	58 (39.5)	2 (1.4)	0
Elevated SGOT (AST)	32 (21.8)	5 (3.4)	2 (1.4)
Elevated SGPT (ALT)	19 (13.0)	9 (6.1)	1 (0.7)

† New or worsening of CTC Grade for any individual patient for whom data is included in the All Grade (1-4) Baseline data cannot be inferred from this table.

CTC grades: neutropenia (grade 1= 1.5-< 2.0 x 10^9 /L, grade 2=1.0 - < 1.5 x 10^9 /L, grade 3 =0.5 -< 1.0 x 10^9/L, grade 4 <0.5 x 10^9/L), thrombocytopenia (grade 1 < LLN - 75.0 x 10^9/L, grade 2=50.0 - <75.0 x 10^9 /L, grade 3=10.0 - <50.0 x 10^9/L, grade 4 <10.0 x 10^9/L), anemia (hemoglobin: grade 1< LLN - 100 g/L, grade 2= 80 - < 100 g/L, grade 3=65 - <80 g/L, grade 4 <65 g/L), elevated creatinine (grade 1 > ULN - 1.5 x ULN, grade 2 > 1.5 - 3.0 x ULN, grade 3 >3.0 - 6.0 x upper limit normal range (ULN), grade 4 >6.0 x ULN), reduced albumin(grade 1 < LLN - 30 g/L, grade 2= 20 - < 30 g/L, grade 3 < 20 g/L, grade 4 -), elevated bilirubin (grade 1 > ULN - 1.5 x ULN, grade 2 > 1.5 - 3 x ULN, grade 3 >3-10 x ULN, grade 4 >10 x ULN), elevated alkaline phosphatase (grade 1 > ULN - 2.5 x ULN, grade 2 > 2.5-5 x ULN, grade 3 >5-20 x ULN, grade 4 >20 x ULN), elevated SGOT or SGPT (grade 1 > ULN - 2.5 x ULN, grade 2 > 2.5 - 5.0 x ULN, grade 3 >5-20 x ULN, grade 4 >20 x ULN).

8.5 Post-Market Adverse Reactions

The following types of ADRs have been reported from post-marketing experience and from additional clinical studies with imatinib mesylate. They include spontaneous case reports as well as serious ADRs from smaller or ongoing clinical studies and the expanded access programs. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to

imatinib mesylate exposure.

Cardiovascular: Thrombosis/embolism[1], pericarditis, cardiac tamponade, anaphylactic shock[1] subdural hematoma[1], thrombotic microangiopathy

Dermatology: Panniculitis (including erythema nodosum), lichenoid keratosis, lichen planus, pemphigus, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic syndromes (DRESS), pseudoporphyria

Digestive: Ileus/intestinal obstruction, tumor hemorrhage/tumor necrosis, gastrointestinal perforation (some fatal cases of gastrointestinal perforation have been reported), diverticulitis, gastric antral vascular ectasia (GAVE)

General: Motor vehicle accidents

Hepatic: Hepatitis, Hepatotoxicity with fatal outcomes (See 7 WARNINGS AND PRECAUTIONS – Hepatic Insufficiency and 9 DRUG INTERACTIONS)

Infections and Infestations: Hepatitis B virus reactivation

Musculoskeletal: Musculoskeletal pain upon treatment discontinuation (including myalgia, pain in extremity, arthralgia, bone pain) following long-term treatment observed in CML patients, osteonecrosis, rhabdomyolysis/myopathy, growth retardation in children.

Neoplasm benign, malignant and unspecified (including cysts and polyps):

Tumor lysis syndrome, some of which were fatal.

Nervous system/ psychiatric: Cerebral edema (including fatalities)

Reproductive: Hemorrhagic corpus luteum / hemorrhagic ovarian cyst

Renal: Chronic renal impairment

Respiratory: Acute respiratory failure (fatal cases have been reported in patients with advanced disease, severe infections, severe neutropenia and other serious concomitant conditions), interstitial lung disease

Special senses: Vitreous hemorrhage

[1] Vascular disorders.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

There is limited data on drug interactions. Since the major metabolic pathway is CYP3A4 mediated and imatinib mesylate is an inhibitor of CYP2D6, caution should be exercised with the

co-administration of CYP3A4 inhibitors, inducers, and substrates, as well as CYP2D6 inhibitors and substrates (see 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Effects on ability to drive and use mNRAines

Reports of motor vehicle accidents have been received in patients receiving imatinib mesylate. Patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with NRA-IMATINIB. Therefore, caution should be recommended when driving a car or operating mNRAinery.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 14 Established or Potential Drug-Drug Interactions

Drug Class	Source of Evidence	Effect	Clinical Comment
Drugs that may increase imatinib plasma concentrations			
Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity	CT	There was a significant increase in exposure to imatinib (mean Cmax and AUC of imatinib increased by 26% and 40%, respectively) in healthy subjects when imatinib mesylate was co-administered with a single dose of ketoconazole (CYP3A4 inhibitor).	Caution is recommended when administering NRA-IMATINIB with inhibitors of the CYP3A4 family (e.g. ketoconazole, erythromycin, clarithromycin, itraconazole, grapefruit juice).
Drugs that may decrease imatinib plasma concentrations			
Substances that are inducers of CYP3A4 activity	CT	Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital) may significantly reduce exposure to NRA-IMATINIB. Administration of rifampin 600 mg daily for eight days to	In patients in whom rifampin or other CYP3A4 inducers are indicated, alternate therapeutic agents with less enzyme induction potential should be considered.

		14 healthy adult volunteers, followed by a single 400 mg dose of imatinib mesylate increased imatinib oral dose clearance by 3.8-fold (90% CI 3.5- to 4.3-fold). Mean C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ decreased by 54%, 68% and 74%, respectively compared to treatment without rifampin. Similar results were observed in patients with malignant gliomas treated with imatinib mesylate while taking enzyme-inducing anti-epileptic drugs (EIAEDs) such as carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, and primidone. The plasma AUC for imatinib decreased by 73% compared to patients not on EIADs.	
Drugs that may have their plasma concentration altered by NRA-IMATINIB			
CYP3A4 Inhibitors, such as: Cyclosporine, Imidazole antifungals, Macrolide antibiotics, Metronidazole	T	There is limited data on drug interactions.	Caution should be exercised with the co-administration of this class of drug.
CYP3A4 Inducers, such as: Antiepileptics, Glucocorticoids, Rifampicin, St. John's Wort	T	There is limited data on drug interactions.	Caution should be exercised with the co-administration of this class of drug.
CYP3A4 Substrates, such as: Busulphan, Calcium-channel blockers, Cyclophosphamide, Cyclosporine, Doxorubicin, Epipodophyllotoxins, Glucocorticoids, Ifosphamide, Imidazole antifungals, Macrolide antibiotics (Azithromycin, Clarithromycin, Erythromycin), PPIs, Retinoic acid, Rifampicin, Serotonin-H3	CT/T	There is limited data on drug interactions. Imatinib mesylate increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5- fold, respectively, suggesting an inhibition of the CYP3A4 by imatinib mesylate. *In vitro*, human liver microsome studies	Caution should be exercised with the co-administration of this class of drug. Caution is recommended when administering NRA-IMATINIB with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporine, pimozide) (see 8 ADVERSE

antagonists, Vinca alkaloids		demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5, and 8 µM, respectively. Imatinib is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5.	REACTIONS).
CYP2D6 Inhibitors, such as: Dextropropoxyphene, Doxorubicin, Quinidine, Vinca alkaloids	T	There is limited data on drug interactions.	Caution should be exercised with the co-administration of this class of drug.
CYP2D6 Substrates, such as: Cyclophosphamide, Beta blockers, Morphine, Oxycodone, Serotonin-H3 antagonists	T	There is limited data on drug interactions. *In vitro*, human liver microsome studies demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5, and 8 µM, respectively. Imatinib is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. *In vitro*, imatinib mesylate inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Imatinib at 400 mg twice daily had a weak inhibitory effect on CYP2D6-mediated metoprolol metabolism, with metoprolol C_{max} and AUC being increased by approximately 23%.	Caution should be exercised with the co-administration of this class of drug. Caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with NRA-IMATINIB and metoprolol clinical monitoring should be considered.
Drugs metabolized by CYP2C9, such as:	T	*In vitro* data suggest that imatinib mesylate has some	Caution should be exercised with the

Warfarin		capacity to act as an inhibitor of CYP2C9, although at concentrations higher than would be expected in plasma with recommended doses.	concomitant use of drugs metabolized by CYP2C9 (e.g. warfarin). In view of the potential interaction between imatinib mesylate and warfarin, the international normalised ratio (INR) of patients who require anticoagulation with warfarin should be monitored closely, especially when NRA-IMATINIB dose adjustments are necessary. Consideration should be given to anticoagulation with low-molecular weight heparin or unfractionated heparin.
Acetaminophen	CT/T	*In vitro*, imatinib mesylate inhibits acetaminophen O-glucuronidation metabolic pathway with Ki value of 58.5mcmol/L. Based on the *in vitro* results, systemic exposure to acetaminophen would be expected to increase when co-administered with imatinib mesylate. A clinical study showed that co-administration of imatinib mesylate (400 mg/day between days two and eight) in the presence of single dose acetaminophen (1000 mg/day on day eight) in CML patients did not alter the pharmacokinetics of acetaminophen. Imatinib mesylate pharmacokinetics was also not altered in the presence of single-dose acetaminophen. However, there are no pharmacokinetic or safety data on the	CAUTION is recommended in patients on the concomitant use of NRA-IMATINIB with acetaminophen

		concomitant use of imatinib mesylate at doses > 400 mg/day or the chronic use of concomitant acetaminophen and imatinib mesylate.	
Methotrexate	CT/T	Imatinib may delay the clearance of methotrexate, particularly when methotrexate is used at high doses (> 500 mg/m^2).	Caution is recommended when NRA-IMATINIB is given concomitantly with methotrexate.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

There were no clinically relevant differences in absorption when imatinib mesylate was administered either with food or in the fasting state. The concomitant use of grapefruit juice should be avoided.

9.6 Drug-Herb Interactions

Co-medications that induce CYP3A4 such as St. John's Wort may significantly reduce exposure to imatinib mesylate. In two published studies, concomitant administration of imatinib mesylate and a product containing St. John's Wort led to a 30 to 32% reduction in the AUC of imatinib mesylate.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Imatinib mesylate is a protein tyrosine kinase inhibitor, which inhibits the Bcr-Abl tyrosine kinase at the *in vitro*, cellular, and *in vivo* levels. The compound selectively inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome-positive chronic myeloid leukemia (CML) and acute lymphoid leukemia (ALL) patients. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows selective inhibition of Bcr-Abl positive colonies from CML patients.

In addition, imatinib is an inhibitor of several receptor tyrosine kinases: the platelet-derived growth factor receptors (PDGFR-α and PDGFR–β), and the stem cell factor (SCF), receptor (c-Kit), and it inhibits the cellular events mediated by these receptors. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating *kit* mutation.

10.2 Pharmacodynamics

In vivo, imatinib inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Constitutive activation of the PDGFR or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of several conditions including MDS/MPD, HES/CEL and DFSP. In addition, constitutive activation of c-Kit or the PDGFR has been implicated in the pathogenesis of SM. Imatinib inhibits signalling and proliferation of cells driven by dysregulated PDGFR, Kit and Abl kinase activity.

Several mechanisms of resistance have been identified from *in vitro* studies of Bcr-Abl positive cell lines. Mechanisms include amplification of the Bcr-Abl gene and overexpression of the multidrug resistance P-glycoprotein. Mutation or amplification of the Bcr-Abl gene has been described in relapsed patients with advanced stage CML.

Prevalence of Abl kinase domain mutations among samples of resistant CML patients varies across studies, likely reflecting variations in time frames for testing, the duration of imatinib exposure, patient selection differences, and perhaps differences in techniques and sensitivity.

The specific clinical relevance of Abl kinase domain mutations in the prognosis and management of patients with CML requires further study. It is likely that mutations will have different clinical phenotypes, with some being subject to higher-dose imatinib therapy, depending on the IC50 of the mutation, and others requiring alternative treatment strategies.

Recent *in-vitro* experiments have indicated that some mutations remain sensitive to imatinib mesylate at high concentrations, other mutants remain unresponsive to dose escalation, which may indicate a kinase-independent, or even Bcr-Abl independent mechanisms of resistance.

Currently identified possible mechanisms of resistance to imatinib mesylate can be categorized in two main groups: the mechanisms where Bcr-Abl is reactivated and cell proliferation remains dependent on Bcr-Abl signaling, and mechanisms where the Bcr-Abl protein remains inactivated by imatinib mesylate but alternative signalling pathways become activated. Whereas the primary resistance to imatinib mesylate seems mostly associated with amplification of the Bcr-Abl gene, secondary resistance (ie. loss of response or progression) appears to be associated with the emergence of mutations of the Bcr-Abl gene (see Table 15):

Table 15 Currently identified mechanisms of resistance to imatinib

Bcr-Abl dependent mechanisms (cells remain dependent of Bcr-Abl signaling)	**Bcr-Abl independent mechanisms (Bcr-Abl is inactivated)**
Amplification of Bcr-Abl gene	Activation of signaling pathways downstream of Bcr-Abl
Mutations of Bcr-Abl preventing correct Bcr-Abl imatinib binding	Clonal evolution with appearance of new chromosomal abnormalities
Efflux of imatinib by PgP associated MDR protein	Activation of leukemogenic pathways unrelated to Bcr-Abl
Protein binding of imatinib (eg. to	

circulating AGP)	

P-gP: Protein–glyco-Protein
MDR: Multidrug Resistance
AGP: Alpha 1-acid glycoprotein

The clinical utility of detecting mutations remains to be demonstrated, since mutations have been described among imatinib mesylate treated patients without evidence of disease progression. In addition, the approNRA to managing resistance will differ by CML disease stage, irrespective of treatment. Clinical and molecular resistance is much more prevalent among patients with blast crisis and accelerated phase CML, than among patients with chronic phase CML.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of imatinib mesylate have been evaluated in 591 patients and 33 healthy subjects over a dosage range of 25 to 1000 mg.

Absorption

Mean absolute bioavailability for the capsule formulation is 98%. The coefficient of variation for plasma imatinib AUC is in the range of 40-60% after an oral dose. When given with a high fat meal the rate of absorption of imatinib was reduced (11% decrease in Cmax and prolongation of t_{max} by 1.5 h), with a small reduction in AUC (7.4%) compared to fasting conditions.

Distribution

At clinically relevant concentrations of imatinib, binding to plasma proteins is approximately 95% on the basis of *in vitro* experiments, mostly to albumin and α_1-acid glycoprotein, with little binding to lipoproteins.

In *in vitro* experiments, the active metabolite, CGP74588, exhibited similar protein binding behaviour to imatinib at clinically relevant concentrations.

Metabolism

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism.

The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib and the terminal half-life is approximately 40 h at steady state. The plasma protein binding of the N-demethylated metabolite CGP74588 was shown to be similar to that of the parent compound in both healthy volunteers and Acute Myeloid Leukemia (AML) patients although there were variabilities in blood distribution and protein binding between AML patients. Some of the AML patients showed a significantly higher unbound fraction of both compounds which led to a higher blood cell uptake.

A phase I study has shown a 4- to 7-fold accumulation of the metabolite CGP74588 at steady

state following once daily dosing, which was greater than the parent drug (See below: plasma pharmacokinetics). This might be due to the fact that CGP74588 is metabolized at a 53% lower metabolic conversion rate compared to imatinib mesylate in human hepatocytes. The reduced metabolic clearance of CGP74588 is further implied by *in vitro* experiments which showed a lower affinity of CGP74588 to CYP3A4 in comparison to STI571.

Elimination

Based on the recovery of compound(s) after an oral ^{14}C-labelled dose of imatinib, approximately 81% of the dose was eliminated within 7 days in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Following oral administration in healthy volunteers, the t½ was approximately 18 hours suggesting that once daily dosing is appropriate. Plasma pharmacokinetic profiles were analyzed in CML patients on Day 1 and on either Day 7 or 28, by which time plasma concentrations had reNRAed steady state. The increase in mean imatinib AUC with increasing dose was linear and dose proportional in the range 25-1000 mg after oral administration. There was no change in the kinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when imatinib mesylate is dosed once daily.

The effect of body weight on the clearance of imatinib is such that for a patient weighing 50 kg the mean clearance is expected to be 8.5 l/h, while for a patient weighing 100 kg the clearance will rise to 11.8 l/h. These changes are not considered sufficient to warrant dose adjustment based on body weight. There is no effect of gender on the kinetics of imatinib.

Special Populations and Conditions

- **Pediatrics:** A total of 31 pediatric patients with either chronic phase CML (n=15), CML in blast crisis (n = 4) or acute leukemias (n=12) have been enrolled in a dose-escalation phase I trial. In this trial the effective dose in pediatric patients was not identified. This was a population of heavily pretreated patients; 45% had received prior BMT and 68% prior multi-agent chemotherapy. Newly diagnosed patients or those eligible for bone marrow transplantation were not studied. The median age was 14 years (range 3 to 20 years). Of the 31 patients, n=12 were three to 11 years old at the start of the study, n= 17 were between 12 and 18 years, and only two were more than 18 years old. Patients were treated with doses of imatinib mesylate of 260 mg/m^2/day (n=6), 340 mg/m^2/day (n=11), 440 mg/m^2/day (n= 8) and 570 mg/m^2/day (n=6). Dosing based upon body surface area resulted in some patients receiving higher than the adult therapeutic dose, and the effect of this on pediatric patient safety is limited.

  As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients in both phase I and phase II studies. Dosing in children at 260 and 340 mg/m^2/day NRAieved similar exposure, respectively, as doses of 400 mg and 600 mg in adult patients, although this was based upon a small sample size. The comparison of AUC_{0-24} on Day 8 versus Day 1 at the 340 mg/m^2/day dose level revealed a 1.7- fold drug accumulation after repeated once daily dosing. As in adults, there was considerable inter-patient variability in the pharmacokinetics, and the coefficient of variation for AUC_{0-24} ranged from 21% (260

mg/m^2/day) to 68% (570 mg/m^2/day). The AUC did not increase proportionally with dose within the range of doses examined. The active metabolite, GCP 74588, contributed about 20% of the AUC for imatinib. Total plasma clearance is about 8 - 10 L/h at steady state. The plasma AUC of imatinib is significantly lower (p=0.02) in children at ages between 2 and <12 years old (29.3 ug*hr/mL) than those at ages between 12 and <20 years old (34.6 ug*hr/mL). However, the difference between the two age groups does not seem to be clinically significant, only 15% of difference (geometric mean of 29.3 in children compared to 34.6 in adolescents). The AUC exposure in both age groups falls within the adult AUC($_{0-24h}$) range, between 24.8 and 39.7 µg*h/ml, NRAieved at 400 mg and 600 mg daily doses, respectively.

- **Geriatrics:** Based on population PK analysis, there was an effect of age on the volume of distribution (12% increase in patients > 65 years old). This change is not thought to be clinically significant.
- **Hepatic Insufficiency:** In a study of patients with mild and moderate hepatic dysfunction (Table 16), the mean exposure to imatinib (dose normalized AUC) did not differ significantly compared with patients with normal liver function. There was a tendency toward an increased exposure in patients with severe liver dysfunction (approximately 45% increase compared with patients with normal liver function). In this study up to 500 mg daily was used in patients with mild liver dysfunction, up to 400 mg daily in patients with moderate, and up to 300 mg daily in patients with severe liver dysfunction.

  In the severe liver dysfunction group 29% of patients experienced serious adverse events at the 100 mg dose level, 60% at the 200 mg and 50% of patients treated at the 300 mg dose levels. (See sections 7 WARNINGS AND PRECAUTIONS – Hepatic Insufficiency and 4.2 Recommended Dose and Dosage Adjustment – Hepatic Impairment)

Table 16 Liver Dysfunction Classification

Liver Dysfunction	Liver Dysfunction Tests
Mild	Total bilirubin: = 1.5 ULN SGOT: >ULN (can be normal or <ULN if Total bilirubin is >ULN)
Moderate	Total bilirubin: >1.5-3.0 ULN SGOT: any
Severe	Total bilirubin: >3-10 ULN SGOT: any

ULN=upper limit of normal for the institution
SGOT= serum glutamic oxaloacetic transferase

- **Renal Insufficiency:** Imatinib and its metabolites are not excreted via the kidney to a significant extent.

  In a study of patients with varying degrees of renal dysfunction (mild, moderate and severe - see Table 17 below for renal function classification), the mean exposure to imatinib (dose normalized AUC) increased 1.5- to 2-fold compared to patients with normal renal function, which corresponded to an elevated plasma level of AGP, a protein to which imatinib binds strongly. There was a correlation with the incidence of serious adverse events and decreasing renal function (p = 0.0096). In this study, 800 mg daily was used in patients with mild renal dysfunction and 600 mg daily was used in patients with moderate renal dysfunction. The 800 mg dose was not tested in patients with moderate renal dysfunction due to the limited number of patients enrolled. Similarly, only 2 patients with severe renal dysfunction were enrolled at the low (100 mg) dose, and no higher doses were tested. No patients on hemodialysis were enrolled in the study. Since the effect of imatinib mesylate treatment on patients with severe renal dysfunction and on hemodialysis has not been sufficiently assessed, treatment of these patients with imatinib cannot be recommended. Patients with mild or moderate renal dysfunction should be treated with caution, and be given the minimum recommended dose of 400 mg daily as starting dose. The dose should be reduced if not tolerable. If tolerated, the dose can be increased for lack of efficacy. Dosing of patients with moderate renal insufficiency at 800 mg cannot be recommended as this has not been investigated (see sections 8 ADVERSE REACTIONS; 4.2 Recommended Dose and Dosage Adjustment – Renal Impairment; 7 WARNINGS AND PRECAUTIONS – Renal Insufficiency).

Table 17 Renal function classification

Renal dysfunction	Renal function tests
Mild	CrCL = 40-59 mL/min
Moderate	CrCL = 20-39 mL/min
Severe	CrCL = < 20 mL/min

CrCL = Creatinine Clearance

11 STORAGE, STABILITY AND DISPOSAL

Store NRA-IMATINIB at room temperature (15-30°C). Protect tablets from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

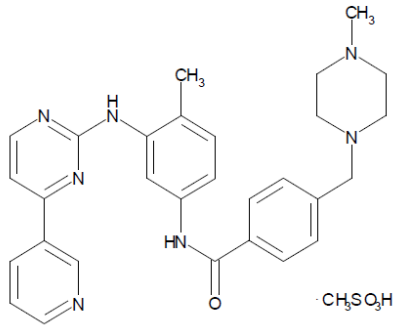
PART 2: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Imatinib mesylate
Chemical name:	(4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino] phenyl]benzamide methanesulfonate)
Molecular formula and molecular mass:	$C_{29}H_{31}N_7O$. CH_4SO_3 and 589.7 g/mol

Structural formula:



Physicochemical properties:

- Description: White to off-white to brownish or yellowish tinged powder
- Solubility: Very to freely soluble in water and aqueous solutions at low pH values. The solubility drops in aqueous buffer solution to “insoluble” with an increase of the pH from pH 5.5 to 8.0.
- pH: The pH of a 1% solution in water is approximately 5.5
- Melting range: 210-220°C (beta crystal form)
- pKa: 7.8, 3.8, and 3.3
- Distribution coefficient: >100 (n-octanol/phosphate buffer pH 6.8 medium at 37±1°C). Log D = 3.5

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Chronic Myeloid Leukemia

Newly diagnosed chronic myeloid leukemia (adults)

Trial Design and Study Demographics

An open label, multicenter, international randomized phase III study has been conducted in adult patients with newly diagnosed chronic myeloid leukemia (CML) in which imatinib mesylate was compared to a combination of interferon-α plus cytarabine (IFN+Ara-C). Patients showing a lack of response [lack of complete hematologic response (CHR) at six months, increasing white blood cell (WBC) counts or no major cytogenetic response (MCyR) at 24 months], loss of response (loss of CHR or MCyR) or severe intolerance to treatment were allowed to cross over to the alternate treatment arm.

In the imatinib mesylate arm, patients were treated with 400 mg daily. Dose escalations were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. In the IFN+Ara-C arm, patients were treated with a target dose of IFN of 5 MU/m^2/day subcutaneously. In addition, subcutaneous Ara-C, (20 mg/m^2/day), was administered for ten days every month until a complete cytogenetic response (CCyR) had been NRAieved and confirmed by cytogenetic analysis on two consecutive occasions not more than three months apart. In this trial, at least 80% of patients were brought to baseline conditions by previous treatment with hydroxyurea. Median WBC decreased from 90 x 10^9/L at diagnosis to 19x10^9/L. Moreover concurrent administration of hydroxyurea during the first six months of the study was permitted in 44.6% and 74.3% of patients in the imatinib mesylate and IFN+Ara-C arms, respectively, to keep the WBC under 20x10^9/L.

A total of 1106 patients were randomized at 177 centers in 16 countries, 553 to eNRA arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18 to 70 years), with 21.9% of patients 60 years of age or older. There were 59% males and 41% females: 89.9% Caucasian and 4.7% Black patients. At an analysis 7 years after the last patient had been recruited, the median duration of first-line treatment was 82 months and 8 months in the imatinib mesylate and IFN + Ara-C arms, respectively, with 60% of patients randomized to imatinib mesylate still receiving first-line treatment. Due to discontinuations and crossover, only 2% of those patients randomized to IFN+Ara-C were still on first-line treatment. In the IFN+Ara-C arm withdrawal of consent (13.7%) was the most frequent reason for discontinuation of first-line therapy. Of the patients who crossed over from the control arm (360/553), the reasons for crossover to the imatinib mesylate arm were intolerance to treatment (N=145, 40.3%), lack of response (N=97, 27.0%), progression (N=77, 21.4%), and patient refusal to continue on IFN + Ara-C (N=41, 11.4%).

Results

The primary efficacy endpoint of the study was progression-free survival. Progression was defined as any of the following events: progression to accelerated phase or blast crisis (AP/BC); death; loss of CHR or MCyR; or an increasing WBC despite appropriate therapeutic management in those patients not NRAieving a CHR. Major cytogenetic response, complete hematologic response, evaluation of minimal residual disease (molecular response), time to accelerated phase or blast crisis, and survival and quality of life were the main secondary endpoints. Response data are provided in Table 18.

Table 18 Response in newly diagnosed CML study (First Line) (84-month data)

Best response rates	Imatinib Mesylate n=553	IFN + Ara-C n=553
Hematological response[1]		
CHR rate n (%)	534 (96.6)*	313 (56.6)*
[95% CI]	[94.7, 97.9]	[52.4, 60.8]
Cytogenetic response[2]		
Major Cytogenetic response n (%)	472 (85.4)*	93 (16.8)*
[95% CI]	[82.1, 88.2]	[13.8, 20.2]
Unconfirmed[3]	490 (88.6)*	129 (23.3)*
Complete Cytogenetic Response n (%)	413 (74.7)*	36 (6.5)
[95% CI]	[70.8, 78.3]	[4.6, 8.9]
Unconfirmed[3]	456 (82.5)*	64 (11.6)*
Molecular response[4]		
Major response at 12 months (%)	40	2
Major response at 24 months (%)	54*	NA[5]

*p<0.001, Fischer's exact test

[1] **Hematological response criteria** (all responses to be confirmed after ≥4 weeks): WBC<$10x10^9$/L; platelet <$450x10^9$/L; myelocyte+metamyelocyte <5% in peripheral blood; no blasts and promyelocytes in peripheral blood; basophils <20%; no extramedullary involvement.

[2] **Cytogenetic response criteria:** complete (0% Ph+metaphases or partial (1-35%).

[3] Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.

[4] **Major molecular response criteria:** in the peripheral blood, reduction of ≥ 3 logarithms in the amount of Bcr-Abl transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardized baseline.

[5] Not Applicable: insufficient data, only two patients available with samples

For analysis of long-term outcomes patients randomized to receive imatinib mesylate were compared with patients randomized to receive IFN+ Ara-C. Patients who crossed over prior to progression were not censored at the time of crossover, and events that occurred in these patients following crossover were attributed to the original randomized treatment.

With 7 years of follow-up, there were 93 (16.8%) progression events in the imatinib mesylate arm: 37 (6.7%) involving progression to AP/BC, 31 (5.6%) loss of MCyR, 15 (2.7%) loss of CHR or increase in WBC and 10 (1.8%) CML unrelated deaths. In contrast, there were 165 (29.8%) events in the IFN+Ara-C arm of which 130 occurred during first-line treatment with IFN+Ara-C. These progression events in the IFN + Ara-C arm included 61 (11%) involving progression to AP/BC, 31 (5.6%) loss of MCyR, 46 (8.3%) loss of CHR, 18 (3.3%) increase in WBC, and 5 (0.9%) CML-unrelated deaths.

The estimated rate of progression-free survival at 84 months was 81.2% with [95% CI: 78%, 85%] in the imatinib mesylate arm and 60.6% with [95% CI: 56%, 65%] in the IFN+Ara-C arm (p<0.001) (Figure 1).

The estimated rate of patients free of progression to AP or BC at 84 months was significantly higher in the imatinib mesylate arm compared to the IFN+Ara-C arm (92.5% with [95% CI: 90, 95] versus 85.1% with [95% CI: 82, 89], (*p*<0.001 respectively)) (Figure 2).

Figure 1 Time to progression (ITT principle)

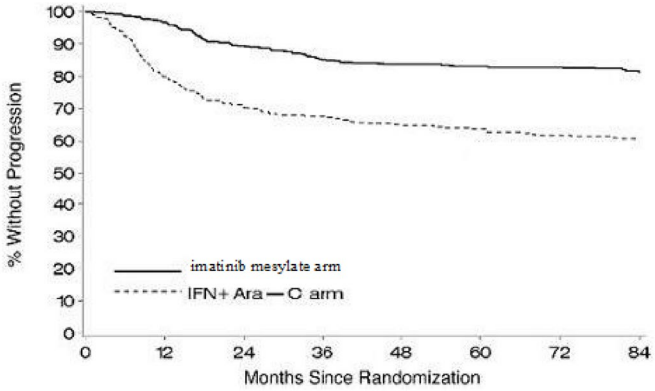
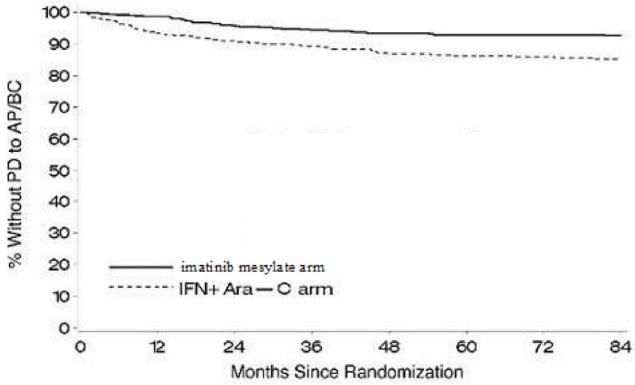


Figure 2 Time to progression to AP or BC (ITT principle)



A total of 71 (12.8%) and 85 (15.4%) patients died in the imatinib mesylate and IFN+Ara-C groups, respectively. At 84 months the estimated overall survival is 86.4% [95% CI: 83, 90] vs. 83.3% [95% CI: 80, 87] in the randomized imatinib mesylate and IFN+Ara-C groups, respectively (p=0.073, log-rank test; p=0.065, Wilcoxon test). The probability of remaining progression-free at 60 months was 95% for patients who were in complete cytogenetic response with major molecular response (≥ 3 log reduction in Bcr-Abl transcripts as measured by quantitative reverse transcriptase polymerase chain reaction) at 12 months, compared to 89% for patients in complete cytogenetic response, but without a major molecular response, and 70% in patients who were not in complete cytogenetic response at 12 months (*p*<0.001).

In this study, dose escalation were allowed from 400 mg daily to 600 mg daily, then from 600 mg daily to 800 mg daily. After 42 months of follow-up, half of the patients who had increased the dose due to lack of CHR at 3 months, NRAieved a CHR thereafter. Of the 55 patients who

did not have a dose increase 44 patients (80%) also NRAieved a CHR. Six (50%) of 12 patients with one assessment indicating loss of PCyR or CCyR NRAieved a MCyR after dose increase and 12 (48%) of the 25 patients without dose increase also NRAieved a MCyR. Eleven patients who did NRAieve a complete hematological response at 3 months and a major cytogenetic response at 12 months while on 400 mg daily dose experienced a confirmed (within 4 weeks) loss of their cytogenetic response. Of those, 4 patients did escalate up to 800 mg daily and 2 of them regained a cytogenetic response (1 partial and 1 complete, the latter also NRAieving a molecular response), while out of 7 patients that did not escalate the dose, only one regained a complete cytogenetic response. The percentage of some adverse events were higher in the 40 patients in whom the dose was increased to 800 mg daily compared to the population of patients before dose increase (n=551). These more frequent adverse events included gastrointestinal hemorrhages, conjunctivitis, elevation of transaminases or bilirubin, hematologic toxicities (mainly anemia and thrombocytopenia) and upper respiratory tract infections. Other adverse events were reported with lower or equal frequency.

Quality of Life (QoL) was measured using the validated FACT-BRM instrument. All domains were assessed and showed that patients in the imatinib mesylate arm had significantly higher scores compared to those in the IFN-Ara-C arm. QoL data showed that patients maintain their physical, functional and emotional well-being while on treatment with imatinib mesylate.

Pediatric newly diagnosed chronic myeloid leukemia

A total of 51 pediatric patients with newly diagnosed and untreated CML in chronic phase were enrolled in an open-label, multicenter, single arm phase II trial. Patients were treated with imatinib mesylate 340 mg/m^2/day, with no interruptions in the absence of dose limiting toxicity. Imatinib mesylate treatment induces a rapid response in newly diagnosed pediatric CML patients with a CHR of 80% after 8 weeks of therapy. Those patients for whom cytogenetics was evaluable (46/51) developed a complete cytogenetic response (CCyR) at a rate of 72%. Additionally, partial cytogenetic response (PCyR) was observed in 15% adding up to a Major Cytogenetic response (MCyR) rate of 87%. The majority of patients who NRAieved a CCyR developed the CCyR between months 3 and 10 with a median time to response based on the Kaplan-Meier estimate of 5.6 months. Fifteen of these patients who NRAieved CCyR underwent quantitative measurement of BCR-ABL transcript (PCR). Six of these patients (40%) NRAieved a major molecular response (five of which were complete responses). Patients were allowed to be removed from protocol therapy to undergo alternative therapy including hematopoietic stem cell transplantation as this is the known curative option. Thirty one children received stem cell transplantation. Of the 31 children, 5 were transplanted after disease progression on study and 1 withdrew from study during the first week of treatment and received transplant approximately 4 months after withdrawal. Twenty five children withdrew from protocol therapy to undergo stem cell transplant after receiving a median of 9 twenty-eight day courses (range 4 to 24). Of the 25 patients 13 (52%) had CCyR and 5 (20%) had PCyR at the end of protocol therapy.

Late chronic phase CML and advanced stage CML

Three large, international, open-label, uncontrolled phase II studies were conducted in patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in advanced, blast or accelerated phase disease, in myeloid blast crisis or with CML in the chronic phase in patients who were resistant/refractory to or intolerant of prior interferon-alpha (IFN) therapy. About 45% of patients were women and 6% were Black. In clinical studies 38-40% of patients were ≥ 60 years of age and 10-12% of patients were ≥ 70 years of age.

Chronic phase, Interferon-failure

532 patients were treated at a starting dose of 400 mg; The patients were distributed in three main categories according to their response to prior interferon therapy: hematologic failure (29%), cytogenetic failure (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥ 25 x106 IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. The primary efficacy variable of the study was the rate of major cytogenetic response (complete plus partial response, 0 to 35% Ph+ metaphases in the bone marrow). Median duration of treatment was 29 months with 81% of patients treated for ≥ 24 months (maximum = 31.5 months). Efficacy results are reported in Table 16. In this study, 65% of the patients NRAieved a major cytogenetic response (MCyR), which was confirmed in 59% of patients. Complete cytogenetic response (CCyR) was NRAieved in 48% of patients, and was confirmed in 38% of patients.

Accelerated phase

235 patients with accelerated phase disease were enrolled. The first 77 patients were started at 400 mg, the protocol was subsequently amended to allow higher dosing and the remaining 158 patients were started at 600 mg.

The primary efficacy variable was the rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. Median duration of treatment was 18 months with 45% of patients treated for ≥ 24 months (maximum = 35 months). A confirmed hematologic response was NRAieved in 72% of patients (Table 16). Importantly, 27% of patients also NRAieved a major cytogenetic response, which was confirmed in 21% of patients. Complete cytogenetic response was NRAieved in 20% of patients, and confirmed in 16%. For the patients treated at 600 mg, the 24-month estimate of the rate of progression-free survival and overall survival is 50% and 66%, respectively. In a multivariate analysis, a dose of 600 mg was associated with an improved time to progression, independent of platelets ≥ 100 x 10^9/L, blood blasts < 15%, and hemoglobin ≥ 10 g/L.

Myeloid blast crisis

260 patients with myeloid blast crisis were enrolled. 165 (63%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 95 (37%) had not ("untreated patients"). The first 37 patients were started at 400 mg, the protocol was subsequently amended to allow higher dosing and the remaining 223 patients were started at 600 mg.

The primary efficacy variable was the rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. Median duration of treatment was 4 months with 21% of patients treated for ≥ 12 months and 10% for ≥ 24 months (maximum = 35 months). In this study, 31% of patients NRAieved a hematologic response (36% in previously untreated patients and 22% in previously treated patients).

Table 19 Response in other CML clinical studies

	Chronic phase IFN failure 400mg (n=532)	**Accelerated phase 600 mg n=158 400 mg n=77**	**Myeloid blast crisis 600 mg n=223 400 mg n=37**
	% of patients ($CI_{95\%}$)		
Hematologic response[1]	**95% (92.3,96.3)**	**72% (65.3, 69.2)**	**31% (25.2, 36.8)**
Complete hematologic response (CHR)	95%	42%	8%
No evidence of leukemia (NEL)	Not applicable	12%	5%
Return to chronic phase (RTC)	Not applicable	17%	18%
Major cytogenetic response[2]			
Unconfirmed	65% (60.2, 68.5)	27% (21.7, 33.4)	15% (11.2, 20.4)
Confirmed	59% (54.9, 63.4)	21% (16.2, 27.1)	7% (4.5, 11.2)
Complete Cytogenetic response[3]			
Unconfirmed	48%	20%	7%
Confirmed	38%	16%	2%

[1] Hematologic response criteria (all responses to be confirmed after ≥4 weeks):

CHR: Chronic phase study [WBC <10 $x10^9$/L, platelet <450 $x10^9$/L, myelocytes+metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC≥1.5 $x10^9$/L, platelets ≥100 $x10^9$/L, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: same criteria as for CHR but ANC ≥1 $x10^9$/L and platelets ≥20 $x10^9$/L (accelerated and blast crisis studies)

RTC: <15% blasts BM and PB, <30% blasts+promyelocytes in BM and PB, <20% basophils in PB, no extramedullary disease other than spleen and liver (accelerated and blast crisis studies).

BM=bone marrow, PB=peripheral blood

[2] Cytogenetic response criteria: A major response combines both complete and partial responses: complete (0% Ph+ metaphases), partial (1%-35%).

[3] Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study

The median time to hematologic response was 1 month.

In late chronic phase CML, with a median time from diagnosis of 32 months, an estimated 87.8% of patients who NRAieved MCyR maintain their response 2 years after NRAieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC, and estimated overall survival was 90.8% [88.3, 93.2].

In accelerated phase, median duration of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5 months for 400 mg, p=0.0035). An estimated 63.8% of patients who NRAieved MCyR were still in response 2 years after NRAieving initial response. The median survival was 20.9 [13.1, 34.4] months for the 400 mg group and was not yet reNRAed for the 600 mg group (p=0.0097). An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2 years of treatment in the 400 mg vs. 600 mg dose groups, respectively (p=0.0088).

In blast crisis, the estimated median duration of hematologic response is 10 months. An estimated 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after NRAieving their initial response. Median survival was 6.9 [5.8, 8.6] months and an estimated 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.

Acute Lymphoblastic Leukemia

Newly diagnosed Ph+ ALL

Imatinib mesylate, when used as a single agent in an induction phase in a controlled trial of 55 newly diagnosed patients aged 55 years and over (ADE10) resulted in a significantly higher rate of complete hematological remission when compared to chemotherapy induction (96.3% vs. 50%; *p*=0.0001).

Table 20 Effect of imatinib mesylate in newly diagnosed Ph+ ALL patients (600 mg/day)

Study	**ADE10[§] (Controlled study)**	
	Imatinib Mesylate induction	CHT induction
N (evaluable for CHR)	27	26
CHR (%)	96	50*
95% C.I.	81 - 100	30 - 70
N (overall)	28	27
1-year DFS (%)	54	
1-year OS (%)	54	
CHR = complete haematological response CHT = chemotherapy * p<0.01		

[§] after induction (Complete remission was NRAieved as a result of induction treatment in both arms).

Relapsed or refractory Ph+ ALL

In study 0109, a total of 43 patients with relapsed or refractory Ph+ALL received the initial dose of 600 mg and 3 patients with relapsed or refractory Ph+ALL received the initial dose 400 mg.

The results in 3 patients with relapsed or refractory Ph+ALL showed that the initial dose of 400 mg/day was insufficient for NRAieving hematological responses.

Table 21 Effect of imatinib mesylate on relapsed or refractory Ph+ALL (600 mg/day)

	Phase II Study No. 0109 (N=46)[1] N(%)
Confirmed Hematologic Response	12 (26.1)
CHR	4 (8.7)
NEL	1(2.2)
RTC	7 (15.2)
Confirmed Cytogenetic Responses	
MCyR	12 (26.1)
CCyR	7 (15.2)
PCyR	5 (10.9)

[1]43/46 patients were relapsed or refractory Ph+ALL
NEL = No Evidence of Leukemia
CHR = Complete Hematological Response
RTC = Return to Chronic Phase

The median time to hematologic response was 1 month.

The median duration of hematologic response was 3.42 months

The median time to progression in patients started with 600 mg was 2.56 months

Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

One open label, multicentre, phase II clinical trial (Study B2225) was conducted testing imatinib mesylate in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 7 patients with MDS/MPD. These patients were treated with imatinib mesylate 400 mg daily. The ages of the enrolled patients ranged from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported in 12 published case reports and a clinical study. These patients also received imatinib mesylate at a dose of 400 mg daily with the exception of three patients who received lower doses. Of the total population of 31 patients treated for MDS/MPD, 14 (45%) NRAieved a complete hematologic response and 9 (29%) a complete cytogenetic response (39% including

major and partial responses). Of note, the malignancy carried a translocation, usually involving the chromosome t5q33 or t4q12, resulting in a PDGFR gene re-arrangement in 14 evaluable patients. All of these patients NRAieved a hematologic response (12 completely). Cytogenetic response was evaluated in 11 out of 14 patients, all of whom responded (9 patients completely). Only 2 (13%) out of the 16 patients without a translocation associated with PDGFR gene re-arrangement NRAieved a complete hematologic response and one (6%) NRAieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly. Median duration of therapy was 12.9 months (0.8 to 26.7) in the 7 patients treated within Study B2225 and ranged between 1 week and more than 18 months in responding patients in the published literature. Results are provided in Table 22.

Table 22 Response in MDS/MPD

	N	Complete hematologic response	Cytogenetic response
	(Number of patients)	(%)	(%)
Overall population	31	14 (45)	12 (39)
Chromosome t5 involved	12	12 (100)	10 (83)
Chromosome t4 involved	2	2 (100)	1 (50)
Others / no translocation	16	2 (13)	1 (6)
Molecular relapse	1	NE	NE

NE: Not evaluable

Aggressive sub-types of Systemic Mastocytosis (ASM and SM-AHNMD)

One open-label, multicentre, phase II clinical trial (Study B2225) was conducted testing imatinib mesylate in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. This study included 5 patients with aggressive systemic mastocytosis (ASM). The ASM patients were treated with imatinib mesylate 100 mg to 400 mg daily. The ages of these 5 patients ranged from 49 to 74 years. A further 25 patients with ASM aged 26 to 85 years were reported in 10 published case reports and case series. These patients also received imatinib mesylate at doses of 100 mg to 400 mg daily. Of the total population of 30 patients treated for SM, 10 (33%) NRAieved a complete hematologic response and 9 (30%) a partial hematologic response (63% overall response rate).

Cytogenetic abnormalities were evaluated in 21 of the 30 ASM patients treated imatinib mesylate from the published reports and Study B2225. Eight out of these 21 patients had FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion). Patients with this cytogenetic abnormality are most likely to be males and to have eosinophilia associated with their systemic mast cell disease. Two patients had a Kit mutation in the juxtamembrane region (one Phe522Cys and one K509I). Sixteen patients had unknown or no detectable cytogenetic abnormality and 50% NRAieved hematologic responses (7 partial and 1 complete) with imatinib mesylate. Four patients showed a D816V c-Kit mutation and one with concomitant CML and SM NRAieved a

complete hematologic response with imatinib mesylate. The majority of ASM patients reported in the reviewed published medical literature with the D816V c-Kit mutation are not considered sensitive to imatinib mesylate. Median duration of imatinib mesylate therapy for the 5 ASM patients in Study 2225 was 13 months (range 1.4-22.3 months) and ranged between 1 month and more than 30 months in the responding patients reported in the published medical literature. A summary of the response rates to imatinib mesylate in ASM is provided in Table 23.

Table 23 Response in ASM

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
FIP1L1-PDGFRα fusion kinase (or CHIC2 deletion)	8	8 (100%)	0 (0%)
Juxtamembrane mutation	2	0 (0%)	2 (100%)
Unknown or no cytogenetic abnormality detected	16	1 (6%)	7 (44%)
D816V mutation	4	1*(25%)	0 (0%)
Overall totals	30	10 (33%)	9 (30%)

*Patient had concomitant CML and ASM

Hypereosinophilic Syndrome and/or Chronic Eosinophilic Leukemia (HES/CEL)

One open-label, multicentre, phase II clinical trial (Study B2225) was conducted testing imatinib mesylate in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. In this study, 14 patients with HES/CEL were treated with 100 mg to 1000 mg of imatinib mesylate daily (the recommended dose for this indication is 100 mg/day to 400 mg/day). The ages of these patients ranged from 16 to 64 years. A further 170 patients with HES/CEL aged 11 to 78 years were reported in 42 published case reports and case series. These patients received imatinib mesylate at doses of 75 mg to 800 mg daily. Results are provided in Table 24.

Table 24 Response in HES/CEL

Cytogenetic abnormality	Number of patients	Complete hematologic response	Partial hematologic response
Positive FIP1L1-PDGFRα fusion kinase	69	69 (100%)	0 (0%)
Negative FIP1L1-PDGFRα fusion kinase	56	12 (21%)	9 (16%)
Unknown cytogenetic abnormality	59	34 (58%)	7 (12%)
Overall totals	184	115 (62%)	16 (9%)

Dermatofibrosarcoma Protuberans (DFSP)

One open label, multicentre, phase II clinical trial (Study B2225) was conducted testing imatinib mesylate in a diverse population of patients suffering from life-threatening diseases associated

with Abl, Kit or PDGFR protein tyrosine kinases. This study included 12 patients with DFSP who were treated with imatinib mesylate 800 mg daily. The primary efficacy endpoint was an objective response rate. The age of the DFSP patients ranged from 23 to 75 years; DFSP was metastatic, locally recurrent following initial resective surgery and not considered amenable to further resective surgery at the time of study entry.

The median duration of therapy in Study B2225 was 6.2 months, with a maximum duration of 24.3 months. In Study B2225, one of the 12 DFSP patients NRAieved a complete response (8%) and 8 patients (66%) NRAieved partial response, 3 of which were rendered disease free by surgery. Responses to treatment are described in Table 25.

Table 25 Response in DFSP

Tumor response	Number of patients (N=12) (Study B2225)	%
Complete response	1	8
Partial response [®]	8 (5+3)	66
Total	9	75

[®] 5 patients made disease free by surgery

A further 6 DFSP patients treated with imatinib mesylate are reported in 5 published case reports. Their ages ranging from 18 months to 49 years. The adult patients reported in the published literature were treated with either 400 mg (4 cases) or 800 mg (1 case) imatinib mesylate daily. The pediatric patient received 400 mg/m^2/daily, subsequently increased to 520 mg/m^2/daily. The approved pediatric dose in CML is 340 mg/m^2/day (rounded to the nearest 100 mg, i.e. not to exceed 600 mg). In the published literature duration of therapy ranged between 4 weeks and more than 20 months. Three (50%) of the 6 patients NRAieved a complete response and 2 (33%) NRAieved partial response, with one of the partial responders then rendered disease free by surgery.

Unresectable and/or Metastatic Malignant Gastrointestinal Stromal Tumors

One phase 2, open-label, randomized multinational study (B2222) was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. These patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of Kit -positive malignant GIST that was unresectable and/or metastatic. Immunohistochemistry was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex method after antigen retrieval.

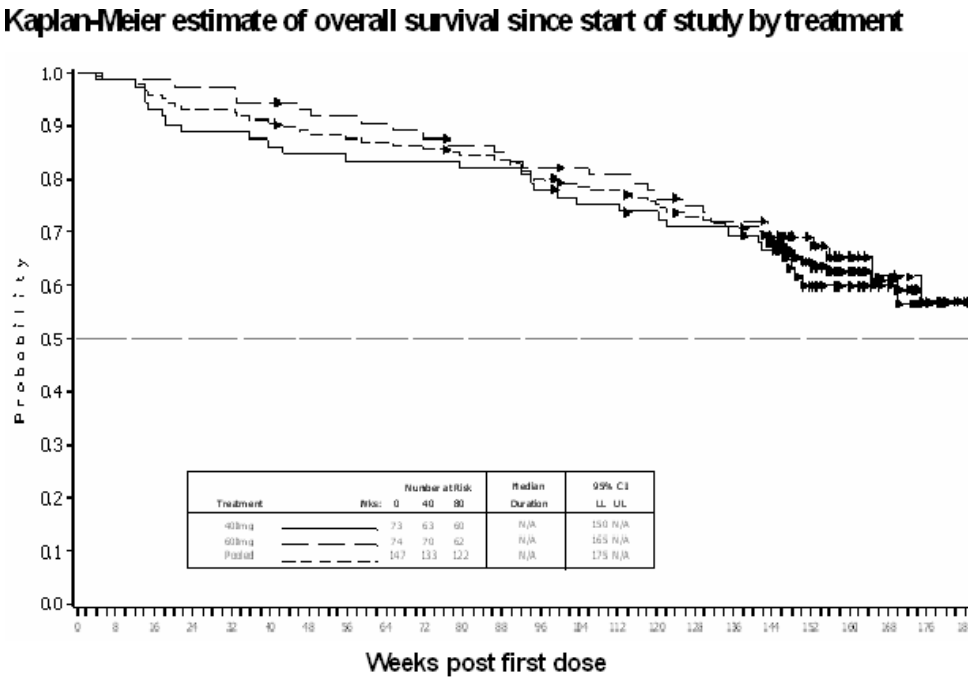
The primary evidence of efficacy was based on objective response rates. Tumors were required to be measurable in at least one site of disease, and response characterization based on Southwestern Oncology Group (SWOG) criteria. Results are provided in Table 26.

Table 26 Best Tumor Response in Trial STIB2222 (GIST)

Best response	All doses (n=147) 400 mg n= 73 600 mg n=74 n (%)
Complete response	1(0.7)
Partial response	98 (66.7)
Stable disease	23 (15.6)
Progressive disease	18 (12.2)
Not evaluable	5 (3.4)
Unknown	2 (1.4)

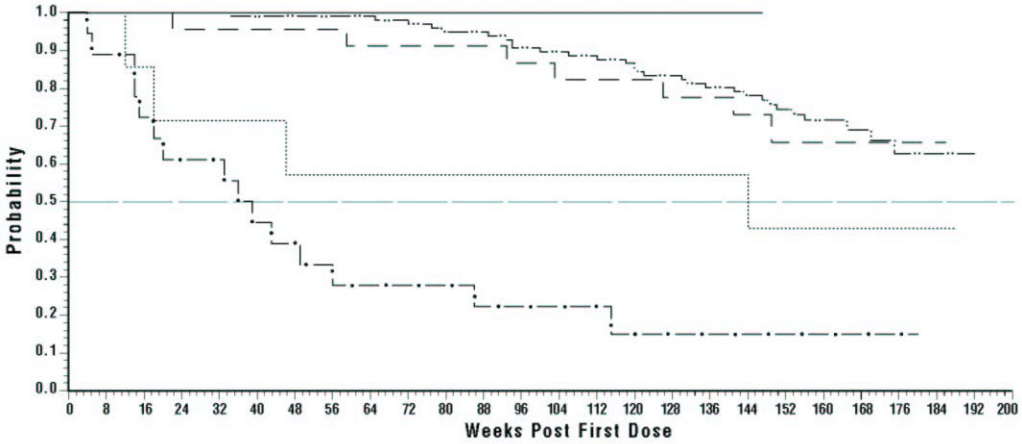
There were no differences in response rates between the two dose groups. A significant number of patients who had stable disease at the time of the interim analysis did NRAieve a partial response with longer treatment (median follow-up 31 months). Median time to response was 13 weeks (95% CI 12 to 23). Median time to treatment failure in responders is 122 weeks (95% CI 106 to 147), while in the overall population is 84 weeks (95% CI 71 to 109). The median overall survival has not been reNRAed. The Kaplan-Meier estimate for survival after 36-months follow-up is 68% (Figure 3).

Figure 3: Kaplan-Meier estimate for survival after 36-months



Hazard ratio: 0.852, Log rank test p=0.5537.

Figure 4: Kaplan-Meier estimate of overall survival since start of study by best response.



Best Response	Wks:	Number at Risk 0	40	80	Median Duration	95% CI LL	UL
CR		1	1	1	N/A	N/A	N/A
PR		98	97	92	N/A	N/A	N/A
SD		23	22	20	N/A	149	N/A
PD		18	8	5	38 Wks	18	56
UNK		7	5	4	144 Wks	18	N/A

Two randomized studies were conducted comparing imatinib mesylate 400 mg versus 800 mg/day as a starting dose: Intergroup Study S0033 and a European-Australian phase III trial (EORTC). Study S0033 showed no significant differences in efficacy between a starting dose of 400 mg and a starting dose of 800 mg daily. The EORTC trial also did not show significant differences in terms of response or overall survival. However, the EORTC trial reported a statistically significant advantage in progression-free survival with the higher dose of imatinib mesylate. Grade 3 to 5 toxicities were described more often in high-dose patients in both studies.

The clinical benefit of dose escalation to 800 mg after progression is uncertain. In three randomized clinical trials (B2222, S0033 and EORTC) the daily dose of imatinib mesylate was escalated to 800 mg in patients progressing at the lower daily dose of 400 mg. A total of 257 escalated their dose to 800 mg daily; 8 patients NRAieved a partial response and 71 patients a stabilization of their disease after dose escalation. The dose escalation in the EORTC study led to a significant increase in anemia and fatigue, although fewer cases of neutropenia were reported after the dose escalation to 800 mg.

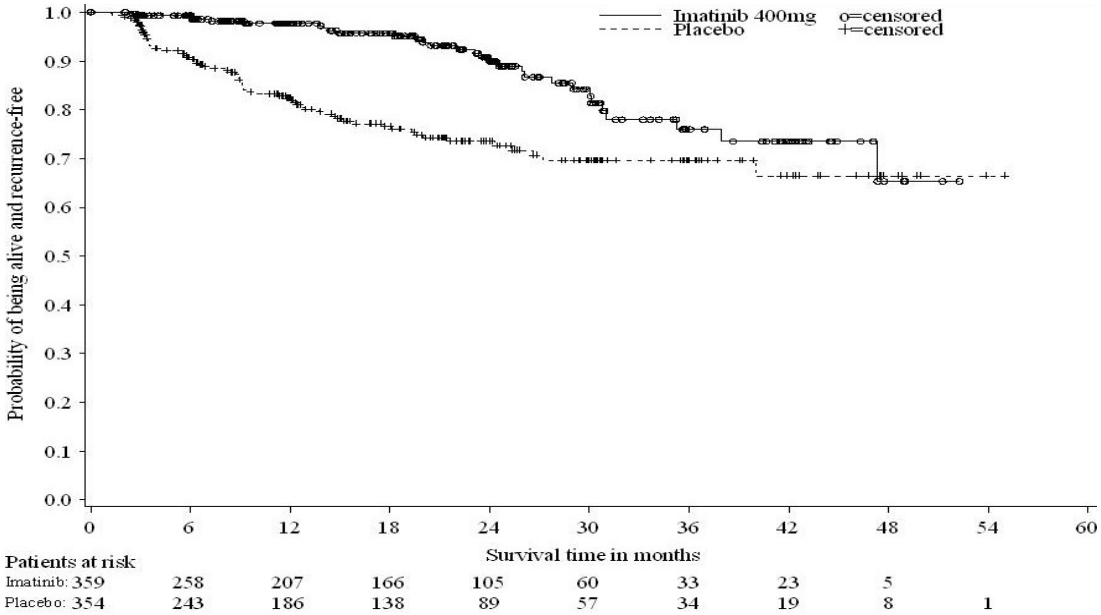
Adjuvant Treatment of GIST

In the adjuvant setting, imatinib mesylate was investigated in a multicentre, double-blind, placebo-controlled, randomized phase III study (Z9001) involving 713 patients. The ages of these patients ranged from 18 to 91 years. Patients who were included had a histologic diagnosis of primary GIST expressing KIT protein by immunochemistry and a tumor size ≥3 cm in maximum dimension, with complete gross resection of primary GIST within 14 to 70 days prior to registration. After complete gross resection of primary GIST, patients were randomized to

one of the two arms: imatinib mesylate at 400 mg/day or matching placebo for one year.

The primary efficacy endpoint of the study was recurrence free survival (RFS) defined as the time from date of randomization to the date of recurrence or death from any cause. At a median follow up of 14.0 months, there had been 30 RFS events in the imatinib mesylate arm and 70 RFS events in the placebo arm (hazard ratio 0.398 [95%CI: 0.259 to 0.610], two-sided log-rank p<0.0001). Based on an interim analysis, the trial was stopped early and placebo patients were allowed to cross over to imatinib mesylate. Overall survival data are immature due to short follow up time

Figure 5 Recurrences Free Survival



Risk of recurrence was also retrospectively assessed in this trial based on the prognostic factors of tumour size, mitotic index, and tumour location. Mitotic index data were available for 556 of 713 patients in the ITT population. The results of subgroup analyses using the United States National Institutes of Health (NIH) and the Armed Forces Institute of Pathology (AFIP) risk classifications demonstrate benefit from use of adjuvant imatinib mesylate in the moderate and high risk groups, but not in the low and very low risk groups. See Table 27:

Table 27 Summary of Z9001 trial RFS analyses by NIH and AFIP risk classifications

RISK CRITERIA	Risk Level	% of pts	#events / #pts	Overall HR (95%CI)[¥]	RFS Rates (%)	
					12 month	24 month
			imatinib mesylate vs. Placebo		imatinib mesylate vs. Placebo	imatinib mesylate vs. Placebo
NIH	Low	29.5	0/86 vs 2/90	N.E.	100 vs 98.7	100 vs 95.5
	Intermediate	25.7	4/75 vs 6/78	0.59 (0.17, 2.10)	100 vs 94.8	97.8 vs 89.5
	High	44.8	21/140 vs 51/127	0.29 (0.18, 0.49)	94.8 vs 64.0	80.7 vs 46.6
AFIP	Very Low	20.7	0/52 vs 2/63	N.E.	100 vs 98.1	100 vs 93.0
	Low	25.0	2/70 vs 0/69	N.E.	100 vs 100	97.8 vs 100
	Moderate	24.6	2/70 vs 11/67	0.16 (0.03, 0.70)	97.9 vs 90.8	97.9 vs 73.3
	High	29.7	16/84 vs 39/81	0.27 (0.15, 0.48)	98.7 vs 56.1	79.9 vs 41.5

[¥]Full follow-up period
N.E = Non Estimate

14.2 Comparative Bioavailability Study

Summary of study establishing bioequivalence of NRA-IMATINIB 400mg Tablets to [Pr]GLEEVEC® 400mg Tablets.

A double-blind, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study comparing NRA-IMATINIB 400 mg Tablets (Nora Pharma Inc.) with [Pr]GLEEVEC® 400 mg Tablets, (Novartis Pharmaceuticals Canada Inc.) was conducted on 36 healthy, adult, human male subjects under fasting conditions.

The summary of results for imatinib from 29 subjects who completed both periods of the study is presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Imatinib (1x 400 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T ** (ng.h/mL)	36695.74 39251.39 (39.7)	35395.99 37130.88 (32.7)	103.5	97.0 – 110.4
AUC_I (ng.h/mL)	38035.08 40549.81 (38.3)	35840.17 37801.43 (33.8)	106.0	100.2 - 112.1
C_{max} (ng/mL)	2112.92 2241.97 (37.2)	1988.09 2077.85 (30.7)	106.2	100.0 - 112.8
T_{max}§ (h)	3.00 (1.33 - 6.02)	3.37 (2.00 - 4.50)		
$t_{½}$€ (h)	15.98 (16.1)	15.95 (16.7)		

*NRA-IMATINIB 400 mg Tablets, manufactured by Intas Pharmaceuticals Limited, India for Nora Pharma Inc.
†PrGLEEVEC® 400 mg Tablets, product of Novartis Pharmaceuticals GmbH, Canada were purchased in Canada.
§Expressed as the median (min - max).
€Expressed as the arithmetic mean (CV%).
**N=23

15 MICROBIOLOGY

N/A

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Subacute and Chronic Toxicity

Study Type	Species	Route	Doses (mg/kg)	Findings
Oral				
26-weeks	Rat	p.o.	5, 15, 50	50 mg/kg: Mortality (2m). Red ears, squinting, swollen appendages, red feet, dry perineal staining, apparent blood or dark yellow urine on cage paper, swollen muzzles and appendages, and dry staining of fur. Slight decrease in body weight (f). Decreased neutrophils, eosinophils, hematocrit, hemoglobin, platelets; increased MCV, MCH, MCHC and red cell distribution width. Increased AST, ALT, total protein, albumin, globulin; decreased A/G ratio, sodium, cholesterol and triglycerides. Increased heart (f), adrenal, liver (m), thyroid (m) and ovary weights; decreased pituitary (f) and testis weights. Enlarged masseter muscles and dark or red ovarian nodules.

				Hemorrhagic and/or cystic corpora lutea, hemosiderin-laden macrophages in ovaries, foamy macrophage accumulation in lungs, focal angiectasis of adrenal cortex, hypertrophy of masseter muscles, focal mineralization/hyperplasia of renal pelvic epithelium and focal new bone formation. [3]15 mg/kg: Prominent eyes, wet perineal staining, increased incidence/frequency of chromodacryorrhea and red penile discharge. Decreased RBC counts and platelets. Increased heart (m) and spleen weights. Focal fibrosis of bone marrow, atrophy of acinar cells of harderian gland, increased eosinophilic macrophages in mesenteric lymph nodes. [3]5 mg/kg: Salivation, presence of oral red substance, chromodacryorrhea, increased incidence/frequency of chromorhinorrhea. Most changes were reversible or partially reversible by the end of the recovery period. NTEL = 5 mg/kg.
13 weeks	Dog	p.o.	3, 10, 30 & 100 reduced to 50	Death in 1 male at 100 reduced to 50 mg/kg. At ≥[3]10 mg/kg, dose-related diarrhea; decreases in RBC counts, and bone marrow hypo-cellularity in some animals; increased ovary weights, hepatic inflammation; gastric & small intestinal changes; thyroid weights decreased with follicular atrophy; increased splenic hemopoiesis. At >30 mg/kg dose-related emesis; decreased WBC, liver toxicity markers in serum; bile duct hyperplasia; pigment deposition in various tissues; thymic atrophy; focal acinar atrophy in the pancreas; reduced spermatogenesis. At high dose decreased testis weight, vacuolation of hepatocytes & bile duct epithelium; cystic corpora lutea containing hemorrhagic fluid; after recovery period peri-biliary fibrosis also present. NOEL = 3 mg/kg.
39-week b.i.d.	Monkey	p.o.	15, 30, 80	Results at 6 months: Twice daily dosing 80 mg/kg: Reduced feces, diarrhea (m, f), and reddened conjunctiva/eyelid, pale gingiva (m). Decreased food consumption and body weight change (f). [3]30 mg/kg: Decreased food consumption and body weight change (m). Reduced albumin. Decreased RBC count, hemoglobin and hematocrit, increased MCV, MCH and MCHC. Presence of Plasmodium species (malaria). [3]15 mg/kg: Soft feces.

Genotoxicity:

The genotoxic potential of imatinib was assessed in a battery of mutagenicity tests. Imatinib was devoid of genotoxicity in bacterial and cellular assays for mutagenic effects. The rat micronucleus assay which detects clastogenic and aneugenic effects was also negative. Positive results were obtained in an *in vitro* assay for clastogenicity (chromosome aberration) in the presence of metabolic activation, but only at concentrations which resulted in significant cytotoxicity.

Carcinogenicity:

In a 2-year rat carcinogenicity study, imatinib was administered in feed at doses of 15, 30 and 60 mg/kg/day and resulted in a statistically significant reduction in the longevity of males rats at 60 mg/kg/day and females rats at ≥30 mg/kg/day. Histopathological examination of decedents revealed cardiomyopathy (both rats sexes), chronic progressive nephropathy (females rats) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were the kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomNRA. The no observed effect levels (NOEL) for the various target organs with neoplastic lesions were established as follows: 30 mg/kg/day for the kidneys, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomNRA, and 15 mg/kg/day for the preputial and clitoral gland.

The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day in rats, representing (approximately 0.5 to 4 times the human daily exposure at 400 mg/day (based on AUC), 0.3 to 2.4 times the human daily exposure at 800 mg/day (based on AUC), and 0.4 to 3.0 times the daily exposure in children at 340 mg/m^2 (based on AUC). The renal adenoma/carcinoma, the urinary bladder and urethra papilloma, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumors of the adrenal glands and the non-glandular stomNRA papillomas/carcinomas were noted only at 60 mg/kg/day.

Non-neoplastic histological lesions not identified in earlier preclinical studies were the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

Reproductive and Developmental Toxicology:

Reproductive toxicity studies indicated that imatinib has a teratogenic potential in rats at doses ^{3}30 mg/kg. A dose of 10 mg/kg appeared to represent the no effect level (NOEL). In rats, doses ^{3}30 mg/kg induced embryo-fetal toxicity and/or teratogenicity (exencephaly, encephalocele, absent or reduced frontal, parietal and/or interparietal bones; dose-dependent protruded tongues) in surviving fetuses. In rabbits, there was no evidence of teratogenicity. Although testes and epididymal weights and percent motile sperm were decreased in male rats at 60

mg/kg, there were no effects on mating or on the number of pregnant females.

Three groups of time-pregnant female rats (n=24/group) were administered STI571 orally by gavage at dosages of 5, 15 and 45 mg/kg/day. The animals were treated from gestation day 6 through lactation day 20.

There was no maternal mortality. A red vaginal discharge was noted in the 45 mg/kg/day group on either day 14 or 15 of gestation. At this dose the number of stillborn pups was slightly increased while the number of viable pups and the number of pups dying between postpartum days 0 and 4 were decreased. In the F1 offspring, at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters NRAieving criterion for preputial separation was slightly decreased. F1 fertility was not affected while an increased number of resorptions and a decreased number of viable fetuses was noted at 45 mg/kg/day. The No Effect Level (NOEL) for both the maternal animals and the F1 generation was 15 mg/kg/day (one-fourth the maximum human dose of 800 mg/day).

Fertility was not affected in the preclinical fertility and early embryonic development study although lower testes and epididymal weights as well as a reduced number of motile sperm were observed in the high dose males rats. In the preclinical pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by imatinib mesylate.

Juvenile Toxicity:

In a juvenile development toxicology study in rats (day 10 to 70 post-partum) administered imatinib, a delay in vaginal opening and preputial separation were observed at approximately 0.3 to 2 times the average pediatric exposure at the highest recommended dose of 340 mg/m^2. Transitory decreases in crown to rump length also were observed (between days 17 and 52 post-partum) in rats administered approximately 2X the highest recommended human pediatric dose of 340 mg/m^2. At this dose, shortened tibia and femur lengths were non-reversible in female rats while a trend towards reversibility was seen in male rats. Furthermore, mortality was observed in juvenile animals (around weaning phase) at approximately 2-times the average pediatric exposure at the highest recommended dose of 340 mg/m^2. Another juvenile study demonstrated that rats administered imatinib resulted in premature growth plate closure.

17 SUPPORTING PRODUCT MONOGRAPHS

1. GLEEVEC® tablet, 100 mg and 400 mg imatinib mesylate, submission control 300958, Product Monograph, Novartis Pharmaceuticals Canada Inc. (JAN 15, 2026)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]NRA-IMATINIB

Imatinib Mesylate Tablets

This Patient Medication Information is written for the person who will be taking **NRA-IMATINIB**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **NRA-IMATINIB**, talk to a healthcare professional.

Serious warnings and precautions box

Take NRA-IMATINIB only under the care of a doctor who knows how to use anti-cancer drugs. They should be trained in how to treat solid tumours or blood cancers.

NRA-IMATINIB can cause serious side effects,

- **Heart disease or problems** where your heart is unable to pump enough blood to meet the body's needs. These include:
  - **Left ventricular dysfunction**
  - **Congestive heart failure**
  - **Cardiogenic shock**
- **Water retention:** a build-up of water in your body
- **Side effects caused by water retention.** These include:
  - **Pleural effusion:** fluid around the lungs
  - **Pulmonary edema:** fluid in the air space of the lungs
  - **Pericardial effusion:** fluid around the heart
  - **Ascites:** fluid in the abdomen
- **Rhabdomyolysis:** a rapid breakdown of muscle. It may lead to sudden kidney failure.
- **Severe bleeding**
- **Liver disorder, jaundice, toxicity or failure.** In some patients, liver failure has led to death.
- **Gastrointestinal perforation**: a hole in the wall of your stomNRA, small or large bowel. In some patients, it has led to death.

What NRA-IMATINIB is used for:

NRA-IMATINIB is used to treat several solid tumour or blood cancer conditions in adults. NRA-IMATINIB can also be used in children for one blood cancer condition.

Ask your healthcare professional if you are not sure why NRA-IMATINIB has been prescribed for you.

How NRA-IMATINIB works:

NRA-IMATINIB helps slow down or stop the growth of cancer cells in your body.

The ingredients in NRA-IMATINIB are:

Medicinal ingredient: Imatinib mesylate

Non-medicinal ingredients: Colloidal anhydrous silica, crospovidone, hypromellose, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and talc.

NRA-IMATINIB comes in the following dosage forms:

Film-Coated Tablets: 100 mg, 400 mg

Do not use NRA-IMATINIB if:

- You are allergic to imatinib or any of the non-medicinal ingredients found in NRA-IMATINIB.
- You are breast-feeding. You must stop breast-feeding before taking NRA-IMATINIB and 15 days after the last dose. It can get into breast milk and harm your baby. Talk to your healthcare professional about the best way to feed your baby during treatment with NRA-IMATINIB.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NRA-IMATINIB. Talk about any health conditions or problems you may have, including if you:

- have heart problems;
- have liver problems;
- have kidney problems;
- have stomNRA problems;
- have bowel problems;
- have bleeding problems;
- have bleeding from your stomNRA, small bowel, or large bowel;
- have your thyroid removed and take a thyroid hormone such as levothyroxine. This may cause your thyroid to be underactive during treatment with NRA-IMATINIB. Your doctor should closely monitor your blood thyroid hormone levels during treatment;
- have ever had or you think you currently have a hepatitis B virus infection (a viral infection of the liver). This is because during treatment with NRA-IMATINIB, hepatitis B may become active again, which can be fatal in some cases. Your healthcare professional will check for signs of this infection before and during treatment with NRA-IMATINIB.

Other warnings you should know about:

Tumour Lysis Syndrome:

- Treatment with NRA-IMATINIB can cause a serious side effect called Tumour Lysis Syndrome (TLS). TLS usually occurs after treatment of a large or fast-growing cancer. As tumour cells die, they release their contents. This leads to high levels of certain chemicals (potassium, uric acid, phosphorous) and low levels of calcium in the blood. High or low levels of these chemicals can cause damage to your organs and may lead to death.
- Some people are at baseline risk of TLS. If your healthcare professional determines this is true for you, prior to starting NRA-IMATINIB, they might give you treatments that may decrease the risk of TLS.

Osteonecrosis:

- Osteonecrosis has been uncommonly reported in adults and children treated with imatinib mesylate. Osteonecrosis is the death of bone tissues due to lack of blood supply. This leads to tiny breaks in the bone and causes the bone to collapse.
- This condition may affect different areas of your body but most commonly affects the hip. Other areas that may be affected include: femur shaft (straight part of your thighbone), shinbone, heel bone, jaw and finger. Talk to your healthcare professional right away if you experience bone or joint pain in any of these areas.
- In serious cases, your healthcare professional will determine if you need to stop taking NRA-IMATINIB and/or undergo surgical treatments.

Female patients:

Pregnancy and birth control

- If you are pregnant or plan to become pregnant, there are specific risks you should discuss with your healthcare professional.
- NRA-IMATINIB can harm your unborn baby. Your healthcare professional may ask you to take a pregnancy test before taking NRA-IMATINIB.
- While taking NRA-IMATINIB, you should use highly effective birth control. Continue taking birth control for 15 days after ending treatment.
- If you become pregnant while taking NRA-IMATINIB, or think you might be, tell your healthcare professional right away.

Male patients:

If you are trying to have a child, talk to your healthcare professional. Your healthcare professional may advise you not to start treatment with NRA-IMATINIB while you are trying to have a child. If you are already taking NRA-IMATINIB, your healthcare professional may advise you to stop taking NRA-IMATINIB before you try to have a child.

Fertility in male patients:

Treatment with NRA-IMATINIB may affect your ability to have children. Talk to your healthcare professional if this is a concern for you.

Driving and using mNRAines:

NRA-IMATINIB can cause vision problems, dizziness or fatigue. Before doing tasks which require special attention, wait until you are feeling well again.

Monitoring and testing:

You will have regular visits with your healthcare professional during treatment with NRA-IMATINIB to monitor your health. They will:

- Weigh you regularly.
- Measure growth in growing children. While taking NRA-IMATINIB, children may grow more slowly.
- Do blood tests and/or urine tests to check how well your kidneys are working. This will be done before you start taking NRA-IMATINIB and during your treatment.
- Do blood tests to check your blood cell counts. This will be done every week for the first month, every 2 weeks for the second month and regularly thereafter (as needed).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NRA-IMATINIB:

- some medicines used to treat fungal infections, like ketoconazole, itraconazole
- some medicines used to treat bacterial infections, like erythromycin, or clarithromycin
- some medicines used to treat epilepsy, like carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin, or primidone
- some medicines used to treat high cholesterol like simvastatin
- some medicines used to treat mental health disorders like pimozide
- some medicines used to treat high blood pressure or heart disorders. This includes metoprolol or a group of medicines called calcium channel blockers
- rifampicin a medicine used to treat tuberculosis (TB)
- St. John's Wort (*Hypericum perforatum*), a herbal product used to treat depression and other conditions
- dexamethasone, a medicine to treat inflammation
- cyclosporine, a medicine that keeps the immune system from rejecting a new organ after a transplant
- acetaminophen, a medicine used to reduce pain or fever — acetaminophen is also included in many cold and flu remedies, so check the label

- warfarin, a medicine used to treat or prevent blood clots
- levothyroxine, if you had your thyroid removed
- grapefruit juice. Do NOT drink grapefruit juice at any time while you are on NRA-IMATINIB.
- methotrexate, a medicine used to treat cancer, rheumatic arthritis, or psoriasis (a chronic skin disease)

If you are already taking NRA-IMATINIB, tell your healthcare professional if you are prescribed a new medicine.

How to take NRA-IMATINIB:

- Take NRA-IMATINIB exactly as your healthcare professional tells you. They will tell you exactly how many tablet(s) to take per day, and how often to take them.
- Take by mouth with food and a large glass of water.

You can take NRA-IMATINIB in one of these two ways:

1. Swallow NRA-IMATINIB:
   a) Whole with a large glass of water.
   b) If the 400 mg tablet is too large to swallow whole:
      - Break it in two pieces
      - Swallow eNRA piece with water, one after the other
2. If you **cannot swallow** a 400 mg tablet broken in two or a 100 mg tablet:
   Place the tablet in a glass with water or apple juice.
   100 mg tablet: use 50 mL or one-quarter cup
   400 mg tablet: use 200 mL or a little less than 1 cup
   - Stir with a spoon to completely dissolve the tablet
   - Drink the whole drink right away
   - Rinse the glass with a little more water or juice and drink that too
   - No trace of the dissolved tablet should be left behind in the glass

Usual dose:

Your healthcare professional will decide the best dosage for you. Your dose depends on if you are an adult or a child, and on your medical condition.

If your daily dose is:

- **600 mg or less:** take once a day, around the same time every day.
- **800 mg:** take twice a day. A 400 mg tablet in the morning and another 400 mg tablet in the evening. To reduce how much iron you get, **use only** the 400 mg tablets to make up your dose.

Your healthcare professional will regularly monitor your condition. They may change your dose depending on how well NRA-IMATINIB is working.

Overdose:

If you think you, or a person you are caring for, have taken too much NRA-IMATINIB, contact a healthcare professional, hospital emergency department, or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you missed a dose OR threw up after taking the last dose, skip the missed dose. Take your next dose at the usual time.

Possible side effects from using NRA-IMATINIB:

These are not all the possible side effects you may have when taking NRA-IMATINIB. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- weight loss, no appetite, change in taste, dry mouth, sores in mouth
- heartburn, indigestion
- constipation, gas, feel bloated
- headNRAe, dizziness
- difficulty sleeping, drowsiness
- weakness, feeling tired
- nosebleeds
- skin dry, itchy or less sensitive to touch
- skin more sensitive to sun
- night sweats, red in the face or other areas of the skin
- unusual hair loss or thinning
- muscle tension, cramps, pain
- bone pain
- joint pain and swelling
- tingling, pain, or numbness in hands, feet, legs
- cough
- increased tears in the eyes, dry eyes.

If any of these affects you severely, tell your healthcare professional.

NRA-IMATINIB can also cause abnormal blood test results.

Children who take NRA-IMATINIB may have the following side effects more often than adults:

- Low blood levels of calcium, sugar, phosphates, albumin protein and sodium
- High blood levels of sugar

Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Water retention: rapid weight gain, swelling of your hands, ankles, feet, face, or eyelids, or your whole body.		√	
Decreased Platelets: bruising, bleeding, fatigue and weakness.		√	
Decreased White Blood Cells: infections, fatigue, fever, NRAes, pains, and flu-like symptoms.		√	
Anemia (Decreased red blood cells): fatigue, loss of energy, weakness, shortness of breath.		√	
Musculoskeletal pain after discontinuing treatment with NRA-IMATINIB: muscle pain, limb pain, joint pain and bone pain.		√	
Common			
Pleural effusion (fluid around the lungs): chest pain. Difficult or painful breathing, cough.			√
Pulmonary edema (fluid in the air spaces of the lungs): difficult breathing that is worse when you lie down. Cough up blood or blood-tinged froth.			√
Pericardial effusion (fluid around the heart): chest pain that feels better when you sit up rather than lie down. Feel light-headed or pass out. Irregular, fast, or forceful heartbeat. Difficult or painful breathing, cough.			√
Ascites (fluid in the abdomen): feeling of fullness, abdominal pain, shortness of breath.			√
Bleeding or swelling in the brain: severe headNRAe. Weak or cannot move arms, legs or face. Difficulty talking, fainting or passing out. Dizziness, blurred vision, seizure (fit).			√
Pneumonia (infection in the lungs): shortness of breath. Difficult and painful breathing, cough, wheezing, or fever.			√
Shortness of Breath	√		
Chest Pain		√	
Inflammatory bowel disease: nausea, vomiting, diarrhea, abdominal pain, fever.		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Liver disorder, jaundice, toxicity, or failure: yellow skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite.			√
Vomiting	√		
Diarrhea	√		
Nausea	√		
Pain in the abdomen	√		
Fever	√		
Less urine, urinate less often.		√	
Eye Infection (conjunctivitis): itchy, red eyes with discharge, and swelling.		√	
Swelling around the eyes or in the eyelids.		√	
Uncommon			
Bleeding in the stomNRA or bowels: severe abdominal pain, vomit blood, black or bloody bowel movement, swelling of the abdomen. Feel dizzy or weak, loss of consciousness. Shortness of breath.			√
Gastrointestinal perforation (a hole in the wall of your stomNRA or bowels): severe abdominal pain, nausea, vomiting, chills or fever.			√
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell.		√	
Interstitial lung disease (diseases that inflame or scar lung tissue): shortness of breath, tiredness, dry cough.			√
Acute respiratory failure: sudden worsening of shortness of breath, bluish color on skin, lips, and fingernails, irregular heartbeats, feel sleepy, loss of consciousness.			√
Low Blood Pressure: dizziness, fainting, light-headedness.		√	
Fainting or passing out		√	
Difficulty hearing		√	
Blood in urine		√	
Left ventricular dysfunction, Congestive heart failure (a weakness of the heart): tiredness, swollen ankles, shortness of breath especially when lying down.			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Heart attack (blood flow stops to part of the heart): sudden chest pain or pressure or discomfort, feeling faint, shortness of breath, possibly irregular heartbeat.			√
Cardiogenic shock (heart is not able unable to pump enough blood to the organs of the body): breathe fast, fast heartbeat, loss of consciousness, sweating, pale skin, cold hands or feet.			√
Angina (not enough oxygen to the heart muscle): chest pain or pressure, usually coming during exercise or physical stress and relieved by rest.			√
Raynaud's syndrome: fingers and toes feel numb and cold in response to cold temperatures or stress.		√	
Cellulitis (infection under the skin): red, hot, painful and swollen area.		√	
Palmar-plantar erythrodysaesthesia syndrome: red or swollen palms of the hands and soles of the feet. You might feel a tingling or burning pain as well.		√	
Tumour lysis syndrome: nausea, shortness of breath, irregular heartbeat, cloudy urine, tiredness, or pain in joints.			√
Osteonecrosis (break down and collapse of bone tissue): pain in bone or joints.		√	
Panniculitis (inflammation of fatty tissue under the skin): painful red lumps on the skin, skin pain, skin reddening.		√	
Rare			
Eye Problems: blood in eye, trouble seeing, blurred vision.		√	
Pulmonary fibrosis (scarring of the lung tissues): shortness of breath, tiredness, dry cough.			√
Seizure		√	
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center. Possibly swollen lips. Mild itching or burning.			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Stevens Johnson syndrome, Toxic epidermal necrolysis (severe skin reaction): rash, red skin, red or purple skin patches possibly with blister or crust in the center, pus-filled rash, peeling skin, blisters on the lips, eyes, skin or in the mouth, itching, burning, flu-like feeling, fever.			√
Breakdown of red blood cells: pale skin, feeling tired or out of breath, dark urine.		√	
Pemphigus: blisters on skin or mucous membranes.		√	
Unknown			
Allergic reactions: itch, rash, hives, swelling of the lips, tongue or throat, difficulty swallowing or breathing.			√
Drug reaction with eosinophilia and systemic symptoms (DRESS) (severe reaction to a medicine. Your skin and one or more of the organs in your body are involved. You may only have some of the side effects that are listed here): fever, severe rash, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinate less often, less urine.			√
Rhabdomyolysis (a rapid breakdown of muscle): unexplained muscle pain, tenderness or weakness. Dark brown urine.		√	
Blood clot in blood vessel: swelling, redness and pain in one part of the body.		√	
Gynecological disorder (problem in woman's reproductive system): pain in lower abdomen or unexpected blood from the vagina or both.		√	
Chronic Kidney Impairment (reduced kidney function).		√	
Hepatitis B virus reactivation (an active viral infection of the liver): Fever, skin rash, joint pain and inflammation as well as tiredness, loss of appetite, nausea, jaundice (yellowing of the skin or whites of eyes), pain in the upper right abdomen, pale stools and dark urine.		√	
Pseudoporphyria (painful blisters on sun-exposed skin; sunburn-type rash).		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thrombotic Microangiopathies (problems related to blood clots in small blood vessels): bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea and acute kidney failure.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store the medication package at room temperature (15°C to 30°C).
- Keep tablets in their original package.
- Protect the tablets from moist air. Make sure the tablets do not get wet.
- Use tablets before the expiry date on the box. Do NOT use tablets after that date.
- If a package is damaged or shows signs of tampering, do NOT use the tablets.
- Keep out of sight and reNRA of children.

If you want more information about NRA-IMATINIB:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: (Drug Product Database: Access the database https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by contacting Nora Pharma Inc., at 1-888-270-9874.

This leaflet was prepared by:
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